

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

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

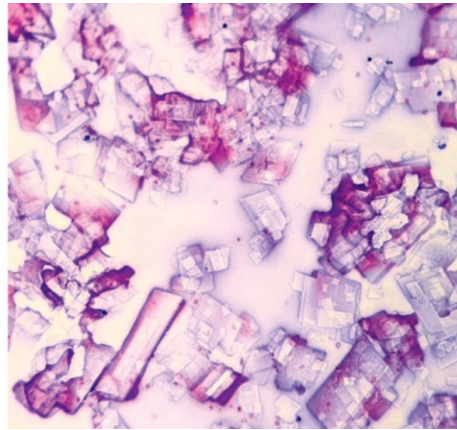
Usually every Wednesday 17:00 - 18:00



### 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!](#)



Examination of the fluid showed numerous polyhedral cholesterol crystals. Additional fluid studies showed an elevated cholesterol level and low triglyceride level. A diagnosis of a tuberculous empyema resulting in a pseudochylothorax was made. Pseudochylous effusions are associated with elevated cholesterol levels, in contrast to chylous effusions, which are associated with elevated triglyceride levels.

A 60-year-old man presented with a 3-month history of cough, dyspnea, and fatigue. On physical examination, decreased breath sounds over the left hemithorax were noted. Computed tomography of the chest showed a large pleural effusion associated with thickening and enhancement of both the parietal and visceral pleura — a finding known as the split pleura sign — and a partially calcified pleural rind. Pleural fluid analysis was consistent with empyema, with an elevated adenosine deaminase level. A polymerase-chain-reaction assay of the pleural fluid was positive for *Mycobacterium tuberculosis*. Which of the following is seen here microscopically in the fluid?

Acid-fast bacilli

Calcium pyrophosphate crystals



Cholesterol crystals

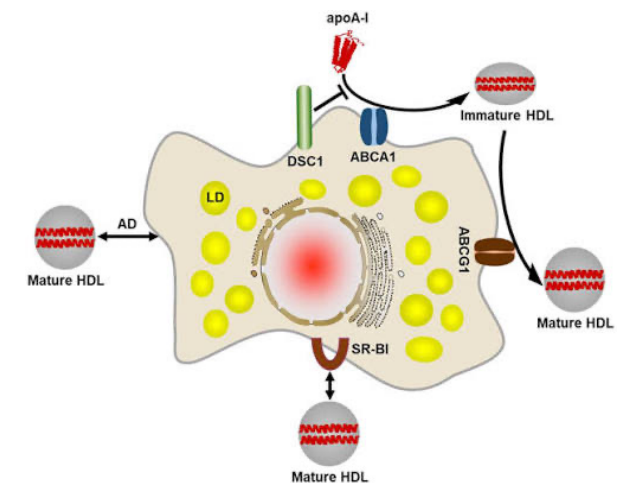
Monosodium urate crystals

Talc

**Cholesterol effusions** (also called pseudochylothoraces or chyloform effusions) develop through chronic pleural inflammation and impaired clearance of lipids from the pleural space.

### Key Mechanisms

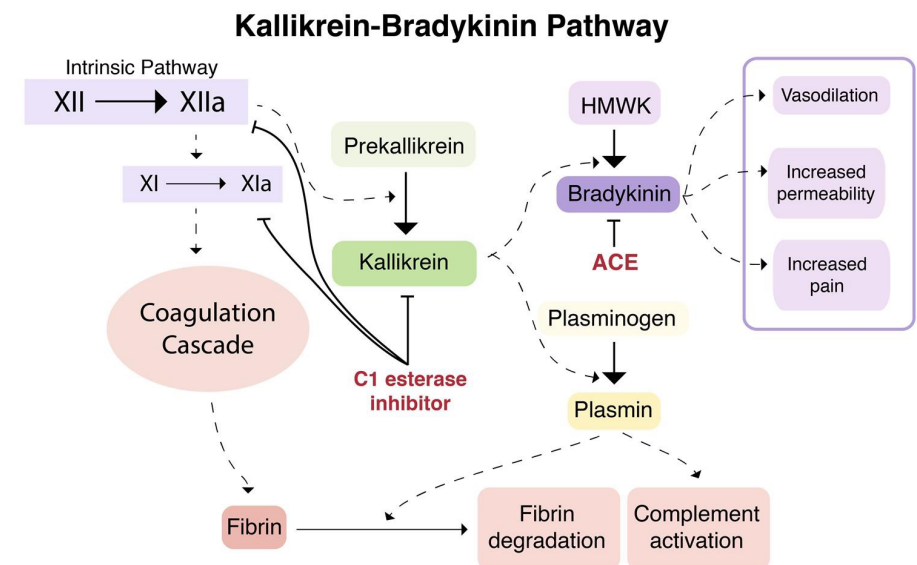
- **Lysis of Cellular Debris:** Chronic inflammation causes the breakdown (lysis) of degenerating red blood cells and white blood cells (neutrophils and leukocytes) inside the pleural fluid, which releases cellular membrane lipids and cholesterol into the space.
- **Thickened Pleural Membranes:** Long-standing pleurisy (frequently linked to conditions like tuberculosis or rheumatoid arthritis) leads to fibrotic, thickened, and sometimes calcified pleural surfaces.
- **Impaired Efflux (Trapping):** The scarred and thickened pleura creates a mechanical barrier with a very low rate of fluid and cholesterol clearance (efflux), trapping the lipid-rich components and allowing them to concentrate over time.
- **Association with High-Density Lipoproteins (HDL):** Biochemical analyses show that the accumulated cholesterol in these pseudochylothoraces is predominantly bound to high-density lipoproteins (HDL) rather than simply floating as free cellular debris.



**Hereditäres Angioödem (HAE)** ist eine seltene, genetisch bedingte Erkrankung, die zu unvorhersehbaren, wiederkehrenden Schwellungen der Haut, der Schleimhäute und der inneren Organe führt.

### Ursachen & Typen

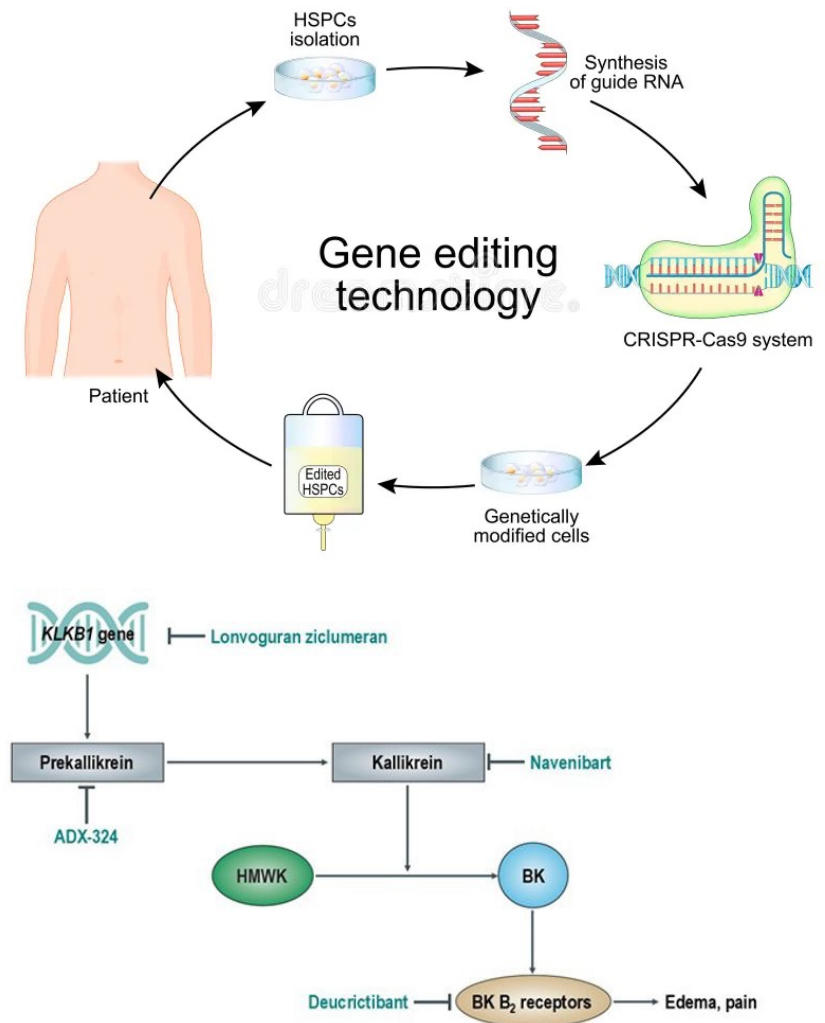
- **Typ I (ca. 85 %):** Zu geringe Menge des C1-Inhibitor-Proteins im Blut.
- **Typ II (ca. 15 %):** Das C1-Inhibitor-Protein ist zwar in normaler Menge vorhanden, aber funktionsunfähig.
- **Typ III (mit normalem C1-Inhibitor):** Beruht auf anderen genetischen Mutationen (z. B. F12, ANGPT1 oder PLG), die ebenfalls zu einem Überschuss des Botenstoffs **Bradykinin** führen (dieser lässt Blutgefäße Flüssigkeit ins Gewebe abgeben).
- **Auslöser:** Verletzungen, Zahnbehandlungen, Operationen, Stress, Infekte oder östrogenhaltige Medikamente.





**Lonvoguran ziclumeran** (bekannt als **lonvo-z** oder **NTLA-2002**) ist eine Prüfpräparat-Therapie, die auf der CRISPR/Cas9-Genbearbeitung basiert.

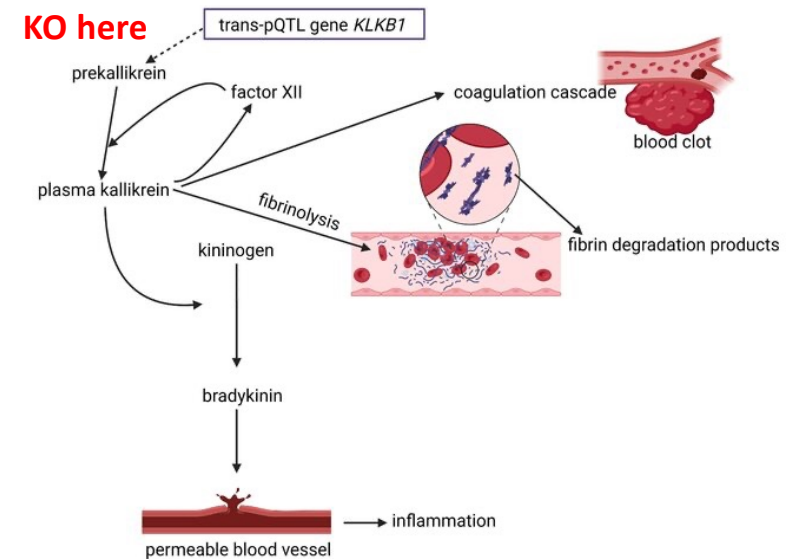
- **Indikation:** Behandlung des hereditären Angioödems (HAE, Typ 1 oder Typ 2) – einer seltenen, genetisch bedingten Krankheit, die schwere Schwellungsanfälle auslöst.
- **Wirkungsweise:** Eine einmalige intravenöse Infusion liefert Lipid-Nanopartikel direkt in die Leber, um das **Gen *KLKB1*** dauerhaft zu inaktivieren und so die Bildung von Plasmakallikrein und Bradykinin zu senken.
- **Studienergebnisse (Phase-3-HAELO-Studie):**
  - Eine einmalige Dosis reduzierte die monatlichen HAE-Anfälle um 87 % im Vergleich zu Placebo.
  - 62 % der Patienten blieben im 6-monatigen Auswertungszeitraum völlig anfalls- und therapiefrei.



Das Gen **KLKB1** (Kallikrein B1) codiert das Protein Präkallikrein (auch bekannt als *Fletcher-Faktor*), eine Vorstufe der Serinprotease Plasmakallikrein. Dieses System spielt eine zentrale Rolle bei der Blutgerinnung, Entzündungsprozessen und der Regulierung des Blutdrucks.

### Biologische Funktion und Aktivierung

- **Synthese:** Das Gen befindet sich auf **Chromosom 4 (4q35.2)**. Das Protein wird primär in den **Hepatozyten der Leber** hergestellt und in die Blutbahn abgegeben.
- **Aktivierungskaskade:** Im Blut zirkuliert Präkallikrein in einem Komplex mit hochmolekularem Kininogen (HMWK). Sobald der **Gerinnungsfaktor XII (Hageman-Faktor)** aktiviert wird (FXIIa), spaltet dieser Präkallikrein in seine aktive Form: **Plasmakallikrein**.
- **Bradykinin-Freisetzung:** Das aktive Plasmakallikrein spaltet wiederum HMWK, wodurch **Bradykinin** entsteht. Bradykinin ist ein hochwirksames Peptid, das die Blutgefäße erweitert (Vasodilation) und die Durchlässigkeit der Gefäßwände (vaskuläre Permeabilität) stark erhöht.



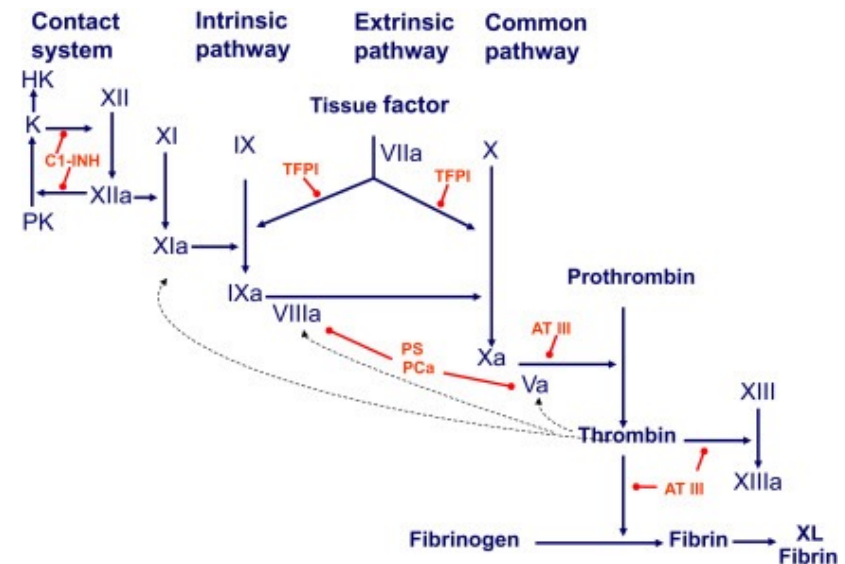
A basic explanation for the role of plasma kallikrein in inflammation and blot clotting. Prekallikrein is encoded by the trans-pQTL gene KLKB1 in the liver. Factor XII converts prekallikrein to plasma kallikrein and leads to the production of more factor XI.

Das Ausschalten (**Knockout**) des **KLKB1-Gens** (welches für Plasma-Präallikrein codiert) führt nicht zu klinischen Blutungsproblemen, sondern schützt stattdessen vor Thrombosen.

Hier sind die wichtigsten Auswirkungen auf die Blutgerinnung im Detail:

### 🔴 **Verlängerte Laborwerte, aber keine Blutungsneigung**

- **Verlängerte aPTT:** Ein Ausfall von KLKB1 führt im Labor zu einer stark verlängerten aktivierten partiellen Thromboplastinzeit (aPTT). Dies liegt daran, dass Präkallikrein ein zentraler Teil des intrinsischen Gerinnungssystems (Kontaktaktivierung) ist.
- **Kein erhöhtes Blutungsrisiko:** Trotz der auffälligen Laborwerte zeigen weder Menschen mit einem angeborenen Präkallikrein-Mangel (Fletcher-Faktor-Mangel) noch *Klkb1*-Knockout-Mäuse eine erhöhte Neigung zu spontanen oder operationsbedingten Blutungen. Das exzessive Blutgerinnungssystem (Gewebefaktor-Weg) kann diesen Ausfall im Körper problemlos kompensieren.



**Lonvo-z (lonvoguran ziclumeran) does not have to knock out both alleles of the *KLKB1* gene in every single liver cell to work.**

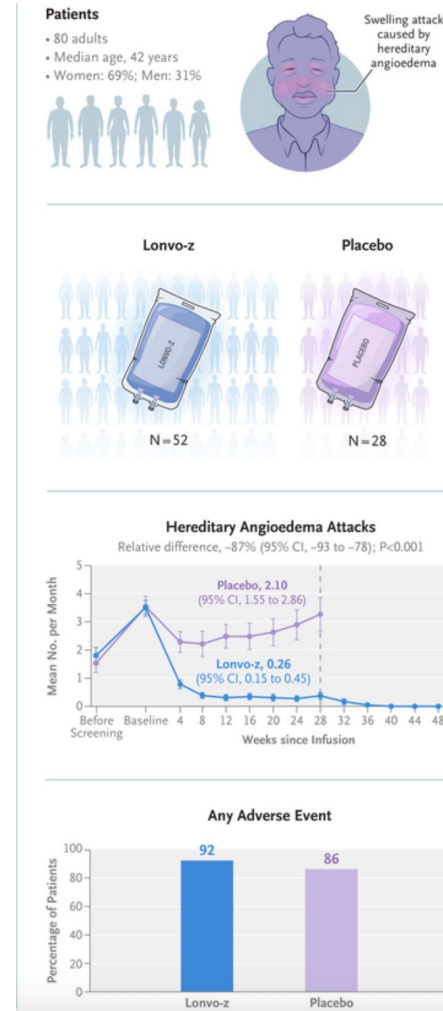
The therapy works on a cumulative, population-wide tissue level rather than requiring absolute cellular perfection:

- **The Goal is a Systemic Drop, Not Complete Elimination:** [Hereditary angioedema \(HAE\)](#) is driven by overactive plasma kallikrein. To stop swelling attacks, [Lonvo-z](#) just needs to decrease the *total pool* of circulating kallikrein protein below a critical threshold.
- **Stochastic (Random) Tissue Editing:** When the lipid nanoparticles deliver the CRISPR-Cas9 machinery to the liver, the editing occurs stochastically across millions of hepatocytes. In a given cell, CRISPR might knock out **both alleles (biallelic)**, just **one allele (monoallelic)**, or miss the cell entirely.
- **High Efficacy from Cumulative Reductions:** Clinical data from [Intellia Therapeutics](#) shows that this combined cellular mixture results in a massive **86% to 96% reduction in overall plasma kallikrein levels**. This deep reduction is more than enough to permanently prevent HAE attacks, proving that a perfect, double-allele knockout in 100% of cells is biologically unnecessary for therapeutic success.

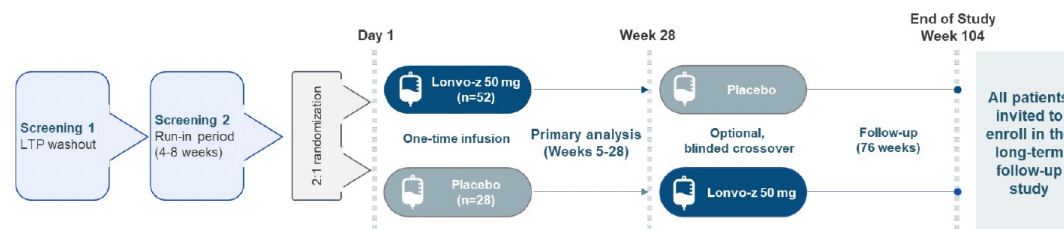


## Lonvoguran Ziclumeran — In Vivo CRISPR Gene Editing in Hereditary Angioedema

Hereditary angioedema is a rare and potentially life-threatening genetic condition characterized by recurrent and debilitating swelling attacks. Lonvoguran ziclumeran (lonvo-z) — an investigational, in vivo gene-editing treatment based on clustered regularly interspaced short palindromic repeats (CRISPR) — is being developed as a single-dose treatment for hereditary angioedema. In a phase 3, double-blind trial, we randomly assigned, in a 2:1 ratio, patients who were 16 years of age or older and had hereditary angioedema with C1 inhibitor deficiency to receive a single intravenous infusion of lonvo-z (at a dose of 50 mg) or placebo. The primary end point was the number of investigator-confirmed hereditary angioedema attacks per month (the monthly attack rate) from week 5 through week 28 after infusion.



Reducing plasma kallikrein production or activity is a clinically validated treatment strategy to reduce bradykinin production, although currently approved treatment options require chronic or on-demand dosing to show efficacy. Plasma kallikrein is derived from prekallikrein, and since the liver is the primary source of prekallikrein, the use of a nonviral, liver-directed lipid nanoparticle to deliver clustered regularly interspaced short palindromic repeats (CRISPR) gene editing in vivo is being investigated as a therapeutic strategy. Lonvoguran ziclumeran (also known as lonvo-z or NTLA-2002) contains CRISPR components — a guide RNA that targets the prekallikrein gene *KLKB1* and a codon-optimized human mRNA sequence of *Streptococcus pyogenes* Cas9 protein. Lonvo-z was designed to reduce the level of plasma prekallikrein by inactivating *KLKB1*, with the intent of resetting the balance of the kallikrein–kinin system and normalizing bradykinin levels. The optimal biologic dose of lonvo-z was identified as 50 mg. Here we report the primary results from HAELO (A Phase 3 Study to Evaluate NTLA-2002 in Participants with Hereditary Angioedema), which evaluated the efficacy and safety of a single intravenous infusion of 50 mg of lonvo-z in patients with hereditary angioedema due to C1 inhibitor deficiency.



**Patients**

Eligible patients were at least 16 years of age, had received a diagnosis of hereditary angioedema due to C1 inhibitor deficiency, and had at least two investigator-confirmed hereditary angioedema attacks during the 4- to 8-week run-in period.

**Randomization and Treatment**

Patients were randomly assigned in a 2:1 ratio to receive a single infusion of lonvo-z at a dose of 50 mg or placebo. The baseline number of attacks per month ( $\leq 3$  or  $> 3$ ) was used as a stratification factor for randomization. On day 1, the infusion was administered intravenously over the course of approximately 4 hours.

**Clinical Assessment**

Each patient recorded angioedema symptoms, attacks, and treatments in an electronic diary that was reviewed by an investigator to confirm whether an event represented a hereditary angioedema attack. Blood samples for pharmacodynamic and pharmacokinetic analyses were obtained. Additional evaluations are described in the protocol.

**Trial End Points**

The primary end point was the time-normalized number of investigator-confirmed hereditary angioedema attacks per month (the attack rate) from week 5 through week 28, with a month defined as 28 days.

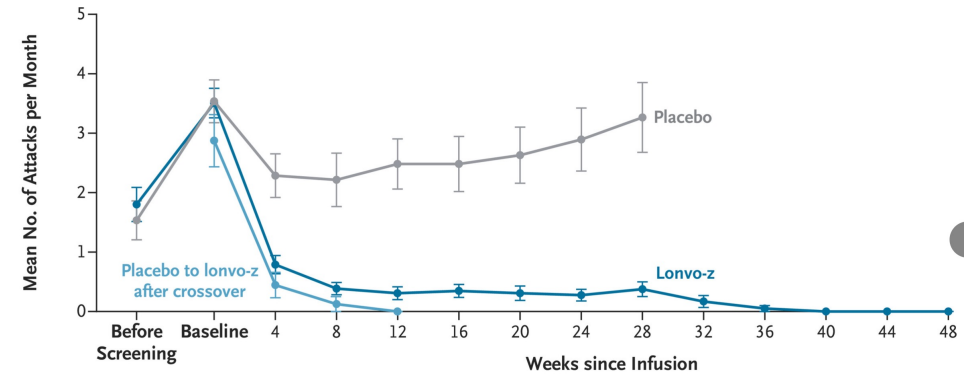
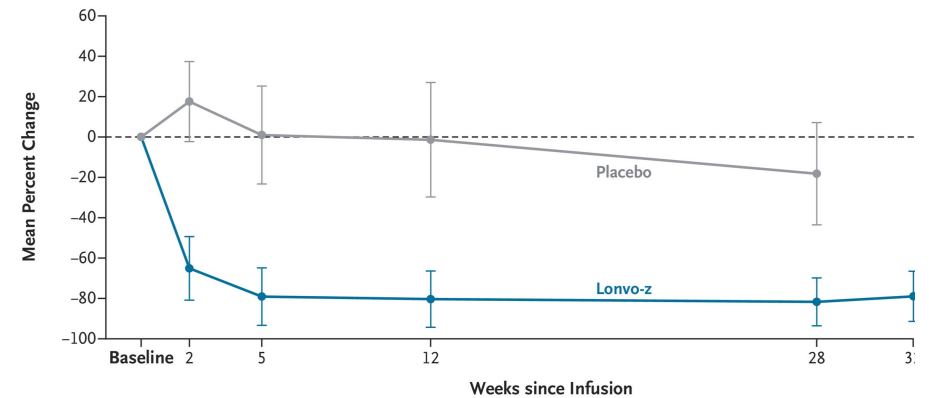
| Characteristic                                                                 | Lonvo-z<br>(N=52) | Placebo<br>(N=28) | All Patients<br>(N=80) |
|--------------------------------------------------------------------------------|-------------------|-------------------|------------------------|
| Median age at screening (range) — yr                                           | 42.0 (23.0–71.0)  | 40.0 (19.0–76.0)  | 41.5 (19.0–76.0)       |
| Sex — no. (%)                                                                  |                   |                   |                        |
| Female                                                                         | 35 (67)           | 20 (71)           | 55 (69)                |
| Male                                                                           | 17 (33)           | 8 (29)            | 25 (31)                |
| Type of hereditary angioedema — no. (%)†                                       |                   |                   |                        |
| C1INH type 1                                                                   | 49 (94)           | 25 (89)           | 74 (92)                |
| C1INH type 2                                                                   | 3 (6)             | 3 (11)            | 6 (8)                  |
| Previous treatment for hereditary angioedema before trial enrollment — no. (%) |                   |                   |                        |
| Long-term prophylaxis‡                                                         | 35 (67)           | 22 (79)           | 57 (71)                |
| On-demand treatment only                                                       | 17 (33)           | 6 (21)            | 23 (29)                |
| Typical severity of angioedema attacks — no. (%)                               |                   |                   |                        |
| Mild                                                                           | 7 (13)            | 5 (18)            | 12 (15)                |
| Moderate                                                                       | 30 (58)           | 20 (71)           | 50 (62)                |
| Severe                                                                         | 15 (29)           | 3 (11)            | 18 (22)                |
| No. of hereditary angioedema attacks per month during the run-in period        | 3.5±1.79          | 3.5±1.91          | 3.5±1.82               |
| AE-QoL total score§                                                            | 58.4±18.05        | 58.0±12.54        | 58.3±16.25             |

## Endpoints

| End Point                                                                                                                       | Lonvo-z<br>(N=52)         | Placebo<br>(N=28)       |
|---------------------------------------------------------------------------------------------------------------------------------|---------------------------|-------------------------|
| <b>Primary end point</b>                                                                                                        |                           |                         |
| LS mean no. of investigator-confirmed hereditary angioedema attacks per month, wk 5 through wk 28 (95% CI)*†‡                   | 0.26 (0.15 to 0.45)       | 2.10 (1.55 to 2.86)     |
| Percent difference vs. placebo (95% CI)                                                                                         | –87 (–93 to –78)          |                         |
| P value                                                                                                                         | <0.001                    |                         |
| <b>Key secondary end points</b>                                                                                                 |                           |                         |
| LS mean no. of investigator-confirmed hereditary angioedema attacks requiring on-demand therapy, wk 5 through wk 28 (95% CI)*†‡ | 0.19 (0.10 to 0.36)       | 1.79 (1.27 to 2.54)     |
| Percent difference vs. placebo (95% CI)                                                                                         | –89 (–94 to –79)          |                         |
| P value                                                                                                                         | <0.001                    |                         |
| LS mean no. of moderate or severe hereditary angioedema attacks, wk 5 through wk 28 (95% CI)*†‡                                 | 0.11 (0.06 to 0.23)       | 1.23 (0.84 to 1.81)     |
| Percent difference vs. placebo (95% CI)                                                                                         | –91 (–96 to –81)          |                         |
| P value                                                                                                                         | <0.001                    |                         |
| Attack-free status, wk 5 through wk 28 — no. (%)†‡                                                                              | 32 (62)                   | 3 (11)                  |
| 95% CI§                                                                                                                         | 47.0 to 74.7              | 2.3 to 28.2             |
| Odds ratio vs. placebo (95% CI)                                                                                                 | 12.81 (3.45 to 47.55)     |                         |
| P value                                                                                                                         | <0.001                    |                         |
| LS mean change from baseline to wk 28 in AE-QoL questionnaire total score — (95% CI)‡¶                                          | –23.51 (–27.64 to –19.38) | –6.47 (–12.26 to –0.68) |
| LS mean difference vs. placebo (95% CI)                                                                                         | –17.04 (–24.15 to –9.93)  |                         |
| P value                                                                                                                         | <0.001                    |                         |

## Adverse events

| Event                                                                         | Lonvo-z<br>(N = 52) | Placebo<br>(N = 28) |
|-------------------------------------------------------------------------------|---------------------|---------------------|
| Any adverse event — no. (%)                                                   | 48 (92)             | 24 (86)             |
| Related to trial regimen                                                      | 37 (71)             | 6 (21)              |
| Any serious adverse event — no. (%)                                           | 0                   | 1 (4) <sup>†</sup>  |
| Adverse events occurring in >5% of patients<br>in the lonvo-z group — no. (%) |                     |                     |
| Infusion-related reaction                                                     | 32 (62)             | 5 (18)              |
| Headache                                                                      | 10 (19)             | 3 (11)              |
| Fatigue                                                                       | 7 (14)              | 3 (11)              |
| Nasopharyngitis                                                               | 7 (14)              | 9 (32)              |
| Back pain                                                                     | 6 (12)              | 3 (11)              |
| Upper respiratory tract infection                                             | 6 (12)              | 2 (7)               |
| Upper abdominal pain                                                          | 5 (10)              | 0                   |
| Abdominal pain                                                                | 4 (8)               | 0                   |
| Influenza                                                                     | 3 (6)               | 1 (4)               |
| Pain in extremity                                                             | 3 (6)               | 0                   |



## Hereditary Angioedema

Rare and potentially life-threatening genetic disorder



16 Years of age or older  
Hereditary angioedema with C1 inhibitor deficiency

Lonvo-z  
50 mg

Placebo



### SECONDARY END POINTS

Moderate or Severe Hereditary Angioedema Attacks  
Week 5 through week 28



### ADVERSE EVENTS

Any Adverse Event during or after Infusion  
Day 1 through week 28



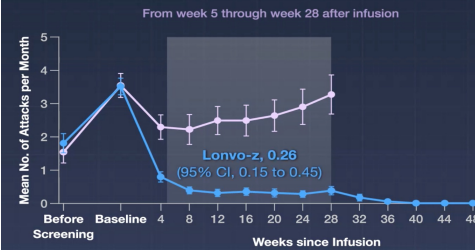
## Lonvoguran Ziclumeran



Investigational, in vivo CRISPR-based gene-editing therapy

### PRIMARY END POINT

Investigator-Confirmed Hereditary Angioedema Attacks per Month  
From week 5 through week 28 after infusion



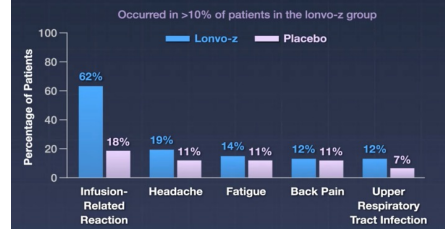
### SECONDARY END POINTS

Attack-free Status  
Week 5 through week 28



### ADVERSE EVENTS

Adverse Events More Common with Lonvo-z than Placebo  
Occurred in >10% of patients in the lonvo-z group

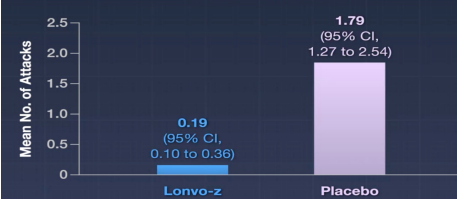


Reduces attack frequency



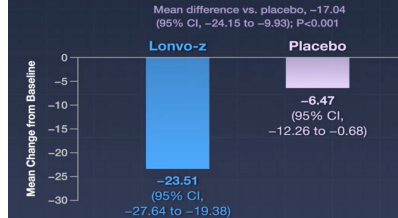
### SECONDARY END POINTS

Investigator-Confirmed Hereditary Angioedema Attacks Requiring On-Demand Therapy  
Week 5 through week 28



### SECONDARY END POINTS

Change from Baseline to Week 28 in the Angioedema Quality of Life Total Score  
Mean difference vs. placebo, -17.04 (95% CI, -24.15 to -9.93); P<0.001

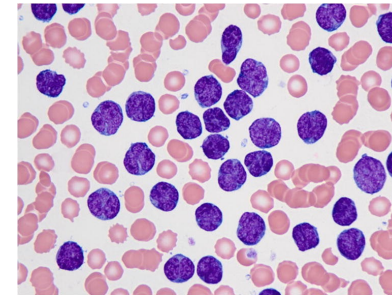
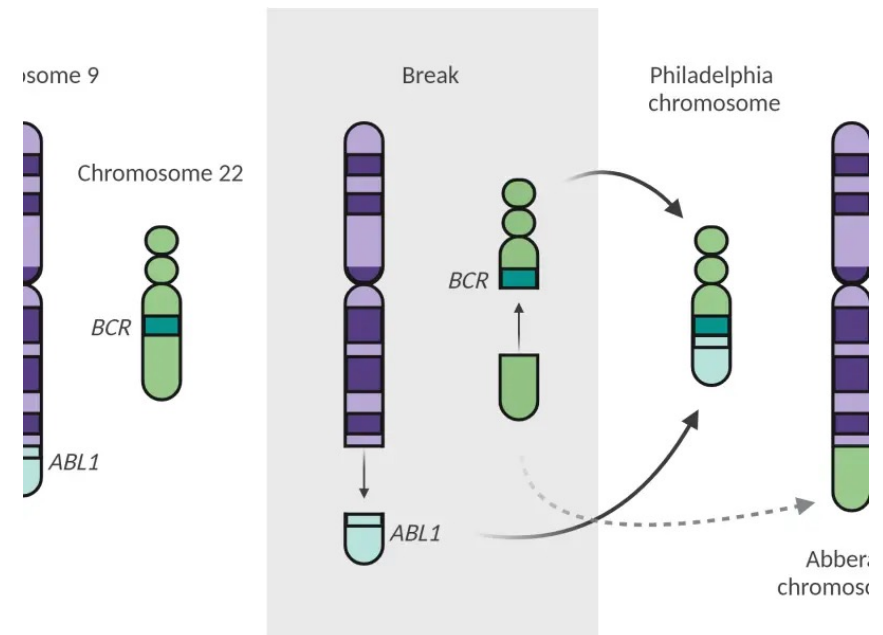


Significantly lower rate of hereditary angioedema attacks



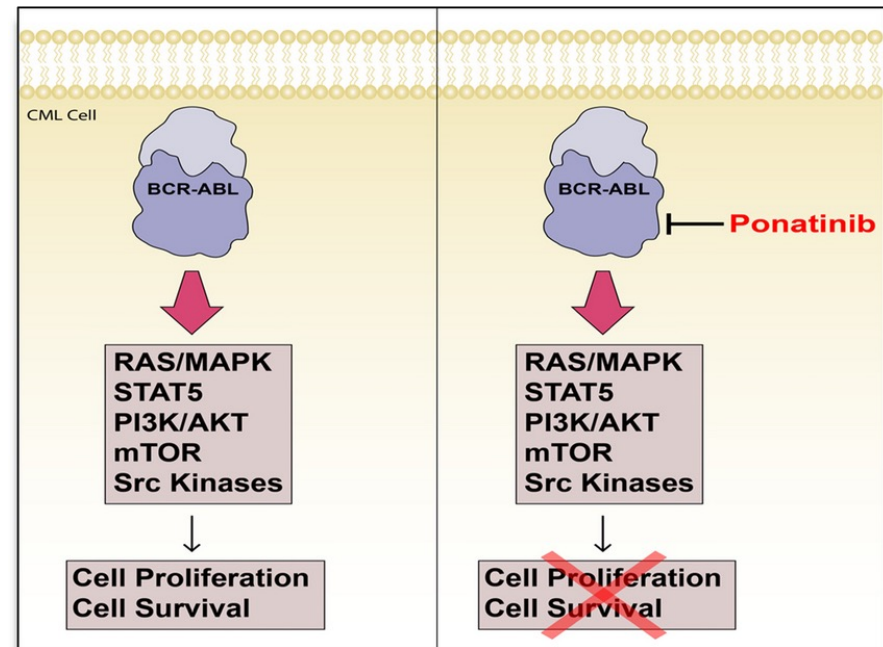
## Was ist Ph-Positive ALL?

- **Die Ursache:** Eine Gen-Verschmelzung (Translokation) zwischen den Chromosomen 9 und 22, die das sogenannte **Philadelphia-Chromosom** erzeugt.
- **Das Genprodukt:** Daraus entsteht das Fusionsgen **BCR::ABL1**, welches ein überaktives Enzym (Tyrosinkinase) bildet. Dieses treibt das unkontrollierte Wachstum von unreifen weißen Blutzellen (Lymphoblasten) an.
- **Häufigkeit:** Es ist die häufigste genetische Untergruppe bei erwachsenen ALL-Patienten (ca. 25 % bis 30% der Erwachsenen) und der Anteil steigt mit dem Alter stark an (bis zu 50 % bei Patienten über 50 Jahren).



**Ponatinib** (Handelsname *Iclusig*) ist ein oraler Tyrosinkinase-Inhibitor der dritten Generation zur Behandlung der chronischen myeloischen Leukämie (CML) und der Philadelphia-Chromosom-positiven akuten lymphoblastischen Leukämie (Ph+ ALL).

- **Anwendungsgebiete:** CML und Ph+ ALL bei Therapieresistenz, Unverträglichkeit gegenüber anderen Tyrosinkinase-Inhibitoren (wie Dasatinib oder Nilotinib) oder bei Nachweis der kritischen **T315I-Mutation**.
- **Wirkmechanismus:** Hemmt die konstitutiv aktive BCR-ABL-Tyrosinkinase sowie zahlreiche resistente Mutationen (einschließlich T315I).
- **Darreichungsform & Einnahme:** Als Filmtabletten (15 mg, 30 mg, 45 mg) oral, unabhängig von den Mahlzeiten, im Ganzen einzunehmen.
- **Dosierung:**
  - In Kombination mit Chemotherapie bei neu diagnostizierter Ph+ ALL: **30 mg einmal täglich**.

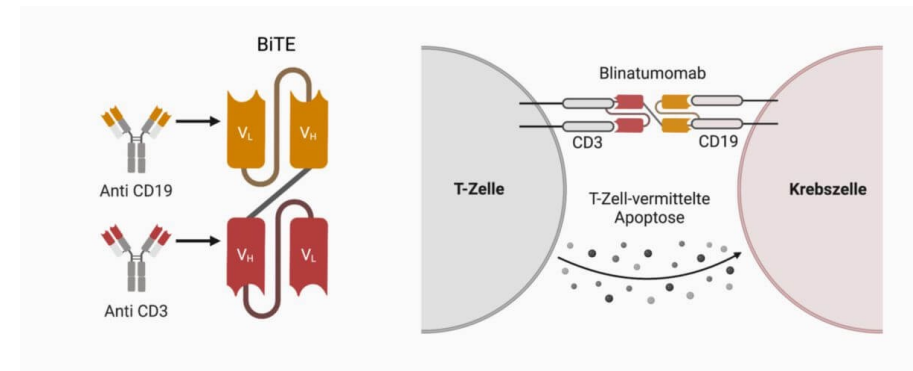


**Blinatumomab** ist ein hochinnovativer, biopharmazeutischer Arzneistoff zur Immuntherapie bei bestimmten Formen der akuten lymphatischen Leukämie (ALL). Er ist der weltweit erste zugelassene Vertreter aus der Gruppe der sogenannten **BiTE-Antikörper** (Bispecific T-cell Engager).

### Wirkungsweise (Wirkmechanismus)

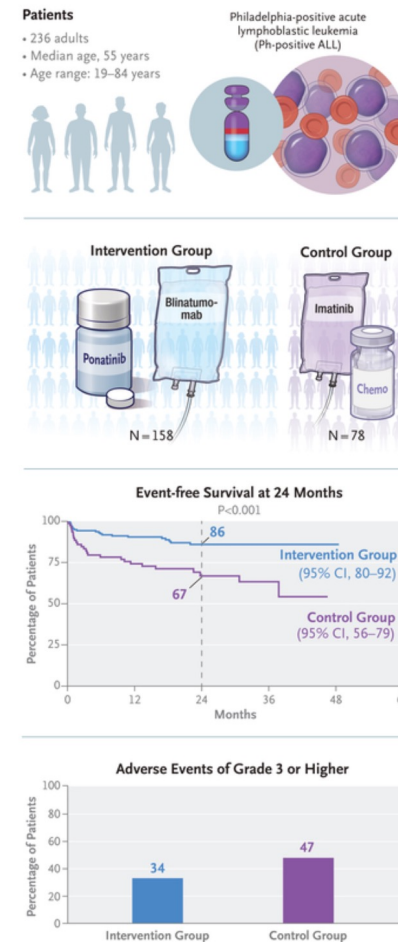
Blinatumomab funktioniert wie eine künstliche Brücke im Immunsystem:

- Als **bispezifischer Antikörper** besitzt er zwei unterschiedliche Bindungsstellen.
- Eine Seite bindet an das Oberflächenprotein **CD19**, das fast ausschließlich auf B-Zellen (und damit auf den bösartigen Leukämiezellen) vorkommt.
- Die andere Seite bindet an den Rezeptor **CD3** auf körpereigenen T-Zellen (den Abwehrzellen des Immunsystems).



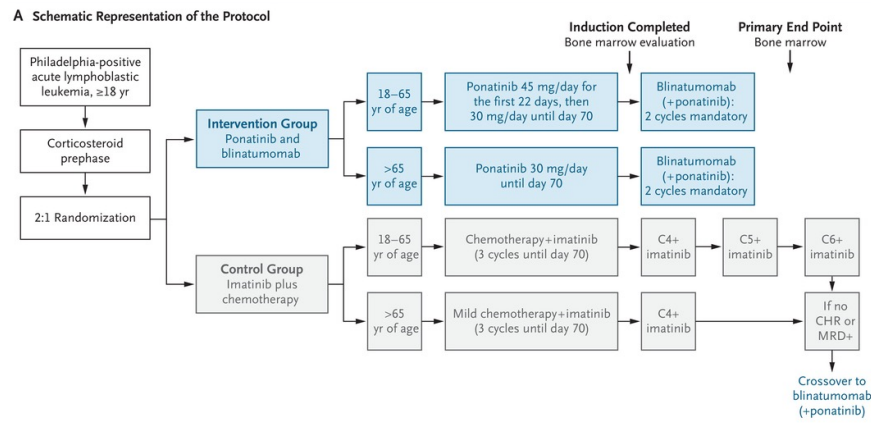
## Ponatinib–Blinatumomab or Imatinib– Chemotherapy for Adult Ph-Positive ALL

The outcome of Philadelphia-positive acute lymphoblastic leukemia (Ph-positive ALL) has greatly improved with the use of tyrosine kinase inhibitors and immunotherapy. In this trial, we randomly assigned adult patients with Ph-positive ALL in a 2:1 ratio to receive ponatinib plus blinatumomab (intervention group) or imatinib plus chemotherapy (control group) as frontline treatment. A crossover to the intervention group was allowed for patients with persistence or reappearance of measurable residual disease in the control group. The primary end point was event-free survival.

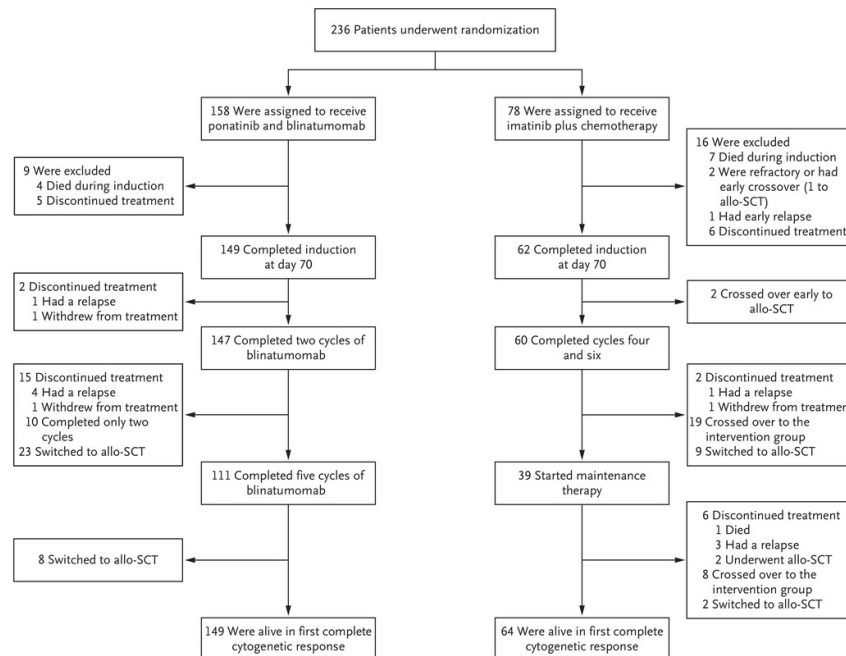


The outcome of Philadelphia-positive acute lymphoblastic leukemia (Ph-positive ALL) has greatly improved since the introduction of tyrosine kinase inhibitors. With the frontline use of imatinib, the first-in-class inhibitor, alone or in combination with chemotherapy, followed by allogeneic hematopoietic stem-cell transplantation when feasible, overall survival increased from 20% to 60%. These results have improved further with the use of second- and third-generation tyrosine kinase inhibitors dasatinib and ponatinib, alone or in combination with chemotherapy. A further substantial improvement has come with the addition of immunotherapy: the bispecific CD19-targeting monoclonal antibody blinatumomab. In the GIMEMA LAL2116 D-ALBA trial, we reported the feasibility of a chemotherapy-free induction-and-consolidation approach with dasatinib, followed by two to five cycles of blinatumomab, in adults ( $\geq 18$  years of age) with newly diagnosed Ph-positive ALL. The long-term follow-up (53 months) showed disease-free, overall, and event-free survival of 75.8%, 80.7%, and 74.6%, respectively.

To formally prove that a chemotherapy-free strategy is superior to a tyrosine kinase inhibitor plus chemotherapy (**mercaptopurine and methotrexate, sometimes combined with periodic vincristine and steroids**), we designed the GIMEMA ALL2820 trial (Sequential Treatment with Ponatinib and Blinatumomab vs. Chemotherapy and Imatinib in Newly Diagnosed Adult Ph-Positive ALL).



**B Enrollment, Treatment, and Outcomes**



## Trial Design, Enrollment, and Outcomes.

Panel A shows a schematic representation of the trial design involving adult patients with Philadelphia-positive acute lymphoblastic leukemia (Ph-positive ALL) in the intervention group and the control group. Patients in the intervention group received ponatinib plus blinatumomab, and those in the control group received imatinib plus chemotherapy. C4 denotes cycle 4, C5 cycle 5, and C6 cycle 6 of administration; CHR denotes complete hematologic response, and MRD measurable residual disease. Panel B shows enrollment of patients, treatment, and outcomes in the trial. The term allo-SCT denotes allogeneic stem-cell transplantation.



## End Points

The primary end point was event-free survival, as determined in a time-to-event analysis. In this composite end point, events included a lack of a complete molecular response, death from any cause, toxic effects, and resistance (including the development of an *ABL1* mutation). A complete molecular response (i.e., an absence of measurable residual disease [MRD]) was defined as a *BCR::ABL1/ABL1* ratio of 0 or a positive nonquantifiable response (i.e., outside the quantitative range) on analysis of bone marrow samples, according to the EuroMRD guidelines.

## Treatment

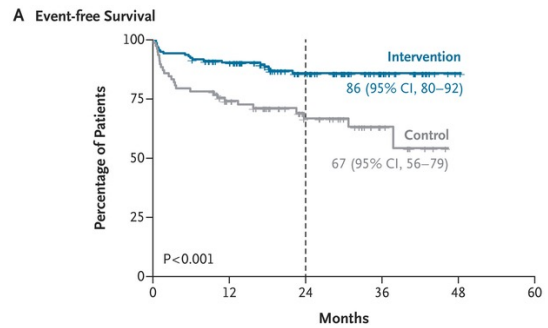
In the two treatment groups, prephase treatment with glucocorticoids was administered at the final dose of 60 mg per square meter of body-surface area in patients who were 65 years of age or younger and 40 mg per square meter in those who were older than 65 years of age, starting from 6 days before the initiation of treatment until final suspension at day 31. In the intervention group, induction consisted of the administration of ponatinib (at a dose of 45 mg daily in patients who were  $\leq 65$  years of age and a dose of 30 mg daily in those who were  $> 65$  years of age) from day 1 to day 70. Treatment continued with at least two cycles of intravenous blinatumomab (at a dose of 28  $\mu\text{g}$  per day) up to a maximum of five cycles, administered concurrently with ponatinib. During the induction and consolidation periods and in the post-consolidation phase, ponatinib was continued. The dose of ponatinib could be reduced in case of toxic effects and if a sustained molecular response occurred.

# Characteristics of the Patients at Baseline.

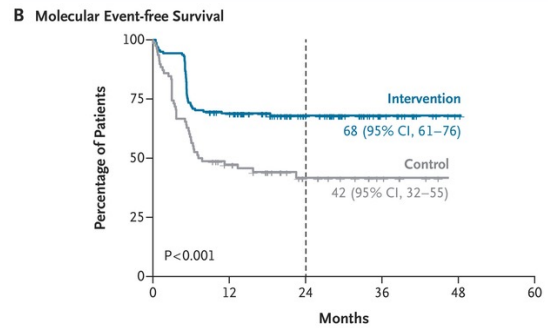
| Characteristic                                                 | Intervention Group<br>(N=158) | Control Group<br>(N=78) |
|----------------------------------------------------------------|-------------------------------|-------------------------|
| Demographic                                                    |                               |                         |
| Age                                                            |                               |                         |
| Median (range) — yr                                            | 57 (19–84)                    | 55 (21–80)              |
| >65 yr — no. (%)                                               | 44 (28)                       | 21 (27)                 |
| Male sex — no. (%)                                             | 79 (50)                       | 46 (59)                 |
| Laboratory values                                              |                               |                         |
| White-cell count                                               |                               |                         |
| Median count per $\mu$ l (range)                               | 10,500 (100–243,600)          | 17,500 (700–231,000)    |
| Distribution — no. (%)                                         |                               |                         |
| >30,000 per $\mu$ l                                            | 43 (27)                       | 23 (29)                 |
| >70,000 per $\mu$ l                                            | 16 (10)                       | 7 (9)                   |
| Median hemoglobin (range) — g/dl                               | 9.2 (4.1–15.5)                | 9.7 (5.1–15.1)          |
| Median platelet count per $\mu$ l (range)                      | 43,000 (8000–458,000)         | 55,000 (8000–546,000)   |
| Category of effect                                             |                               |                         |
| Central nervous system involvement — no. (%)                   | 15 (9)                        | 11 (14)                 |
| Presence of <i>BCR::ABL1</i> transcript — no. (%) <sup>†</sup> |                               |                         |
| p190                                                           | 111 (70)                      | 49 (63)                 |
| p210                                                           | 41 (26)                       | 25 (32)                 |
| p190 and p210                                                  | 6 (4)                         | 4 (5)                   |
| <i>IKZF1</i> plus signature — no./total no. (%) <sup>‡</sup>   | 52/154 (34)                   | 19/74 (26)              |

# Severe Adverse Events.

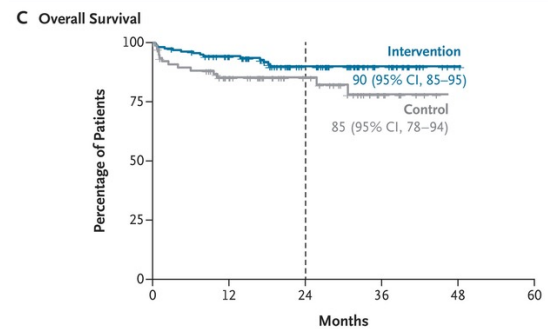
| Group                         | Grade         | Patients<br>with Event | Treatment Phase | Action Taken                                                                  | Relation to Specific Drug†                         |                                                              |
|-------------------------------|---------------|------------------------|-----------------|-------------------------------------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------|
|                               | ≥3            | 5                      |                 |                                                                               |                                                    |                                                              |
|                               | no. of events | no.                    |                 |                                                                               |                                                    |                                                              |
| Intervention                  | 79            | 9                      | 53              |                                                                               |                                                    |                                                              |
| Infection                     | 31            | 2                      | 27              | 4 Events during induction, 12 during consolidation, and 15 during maintenance | 14 Temporary interruptions and 4 withdrawals       | 1 Event with ponatinib and 4 with ponatinib and blinatumomab |
| Cardiovascular event          | 11            | 1                      | 9               | 6 Events during consolidation and 5 during maintenance                        | 14 Temporary interruptions and 4 withdrawals       | 9 Events with ponatinib                                      |
| Decline in general condition‡ | 10            | 1                      | 10              | 2 Events during induction and 8 during consolidation                          | 3 Temporary interruptions                          | 6 Events with blinatumomab                                   |
| Neurologic or psychiatric     | 7             | 1                      | 7               | 1 Event during induction, 2 during consolidation, and 4 during maintenance    | 4 Temporary interruptions and 1 withdrawal         | 1 Event with ponatinib and 2 with blinatumomab               |
| Hepatic                       | 6             | 0                      | 5               | NA                                                                            | 4 Temporary interruptions                          | 5 Events with ponatinib                                      |
| Vascular                      | 3             | 0                      | 3               | 2 Events during consolidation and 1 during maintenance                        | 3 Temporary interruptions                          | 5 Events with ponatinib                                      |
| Gastrointestinal              | 3             | 1                      | 3               | 1 Event during induction and 2 during maintenance                             | 2 Temporary interruptions                          | NA                                                           |
| Control                       | 61            | 7                      | 37              |                                                                               |                                                    |                                                              |
| Infection                     | 14            | 3                      | 13              | 4 Events during induction, 1 during consolidation, and 9 during maintenance   | 6 Temporary interruptions and 4 withdrawals        | 2 Events with chemotherapy                                   |
| Blood or lymphatic            | 10            | 0                      | 10              | 4 Events during induction, 2 during consolidation, and 4 during maintenance   | 1 Temporary interruption and 2 reductions          | NA                                                           |
| Gastrointestinal              | 9             | 1                      | 7               | 3 Events during induction and 6 during maintenance                            | 1 Consent withdrawal and 2 temporary interruptions | NA                                                           |
| Pancreatitis                  | 2             | 0                      | 2               | 2 Events during maintenance                                                   | 2 Temporary interruptions                          | 1 Event with imatinib                                        |
| Decline in general condition‡ | 3             | 1                      | 2               | 1 Event during induction and 1 after crossover                                | 2 Temporary interruptions                          | 1 Event with blinatumomab and 1 with chemotherapy            |
| Neurologic or psychiatric     | 6             | 0                      | 6               | 4 Events during induction, 1 during consolidation, and 1 after crossover      | 1 Temporary interruption and 1 reduction           | 1 Event with blinatumomab and 1 with chemotherapy            |
| Vascular                      | 4             | 0                      | 3               | 2 Events during induction and 2 after crossover                               | 1 Withdrawal and 2 temporary interruptions         | 2 Events with ponatinib and 2 with chemotherapy              |
| Kidney failure                | 3             | 0                      | 2               | 3 Events during maintenance                                                   | NA                                                 | NA                                                           |
| Respiratory                   | 2             | 1                      | 2               | 2 Events during induction                                                     | 1 Withdrawal                                       | 1 Event with imatinib                                        |
| Cardiac                       | 3             | 1                      | 3               | 2 Events during induction and 1 after crossover                               | 1 Temporary interruption                           | 1 Event with ponatinib                                       |



| No. at Risk  |     |     |    |    |   |   |
|--------------|-----|-----|----|----|---|---|
| Intervention | 158 | 133 | 74 | 31 | 1 | 0 |
| Control      | 78  | 52  | 27 | 10 | 0 | 0 |

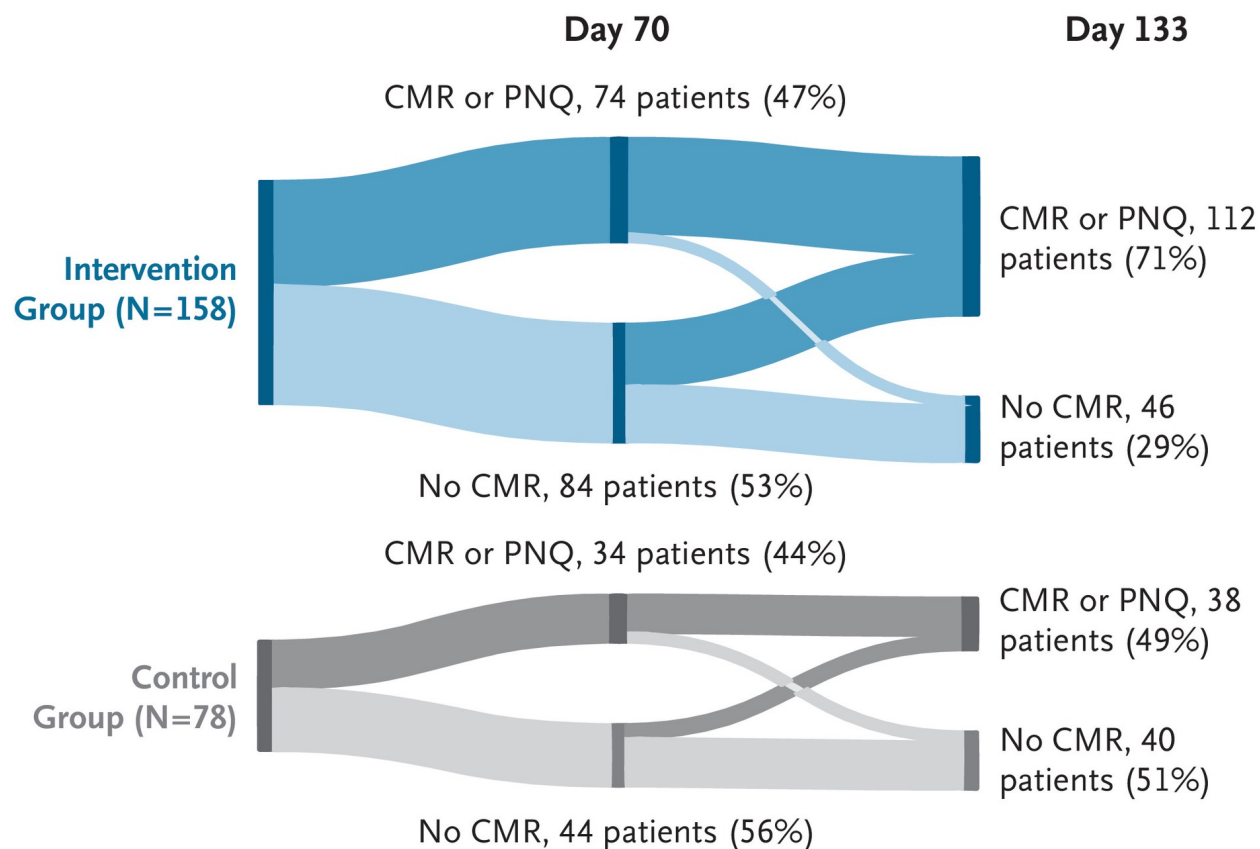


| No. at Risk  |     |     |    |    |   |   |
|--------------|-----|-----|----|----|---|---|
| Intervention | 158 | 102 | 56 | 20 | 1 | 0 |
| Control      | 78  | 33  | 14 | 6  | 0 | 0 |



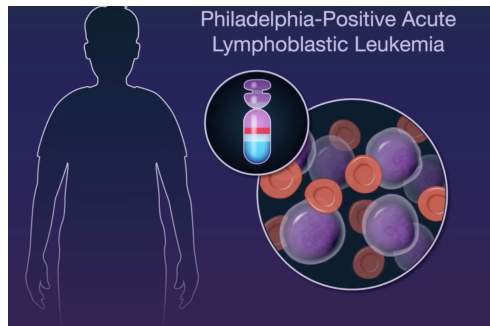
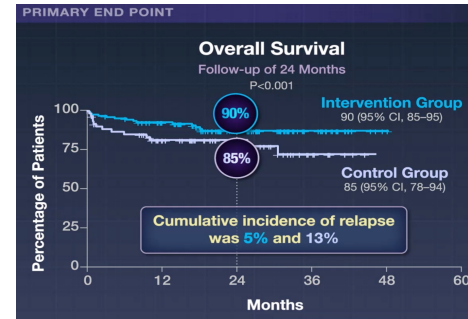
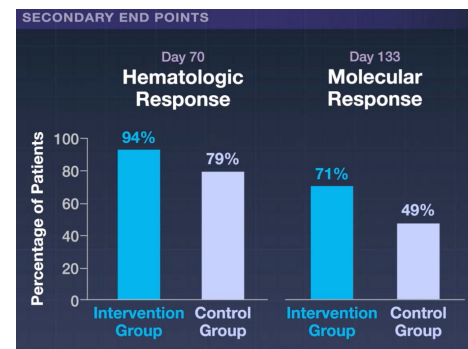
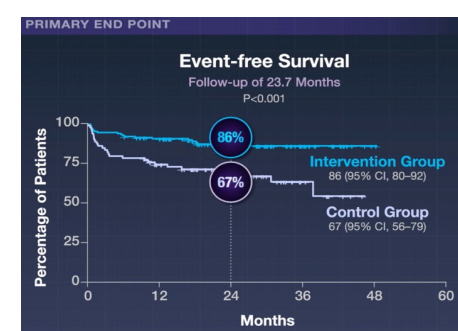
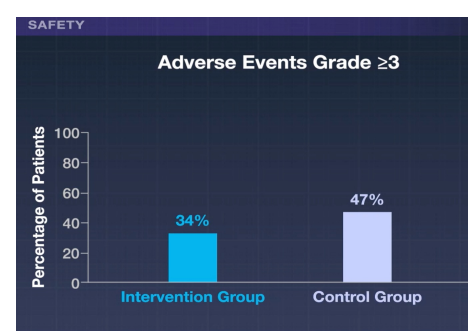
## Survival and Molecular Outcomes with Estimates at 24 Months.

Shown is event-free survival (the primary end point) in the intention-to-treat analysis among patients in the intervention group (who received ponatinib plus blinatumomab) and in the control group (who received imatinib plus chemotherapy) (Panel A), along with molecular event-free survival (which was defined as an absence of measurable residual disease) (Panel B), and overall survival (Panel C).



### Molecular Responses.

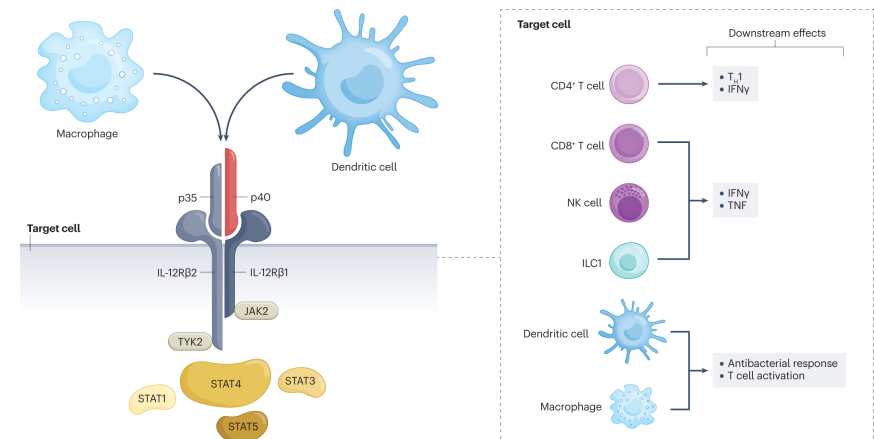
A Sankey plot shows the molecular response to treatment in the intervention group and the control group. A molecular response — which consisted of a complete molecular response (CMR) or a positive nonquantifiable response (PNQ) — occurred in 74 patients (47%) in the intervention group and in 34 patients (44%) in the control group at day 70. (A sample was determined to have a nonquantifiable response if the result was outside the quantitative range.) After consolidation (day 133), a CMR or PNQ was recorded in 112 patients (71%) in the intervention group and in 38 patients (49%) in the control group. Samples are described according to the treatment received in an intention-to-treat analysis.



**Interleukin-23 (IL-23)** ist ein Botenstoff des Immunsystems, der eine zentrale Rolle bei der Entstehung und Aufrechterhaltung von Entzündungen im Darm bei Colitis ulcerosa spielt.

### Die Rolle von IL-23 bei Colitis ulcerosa

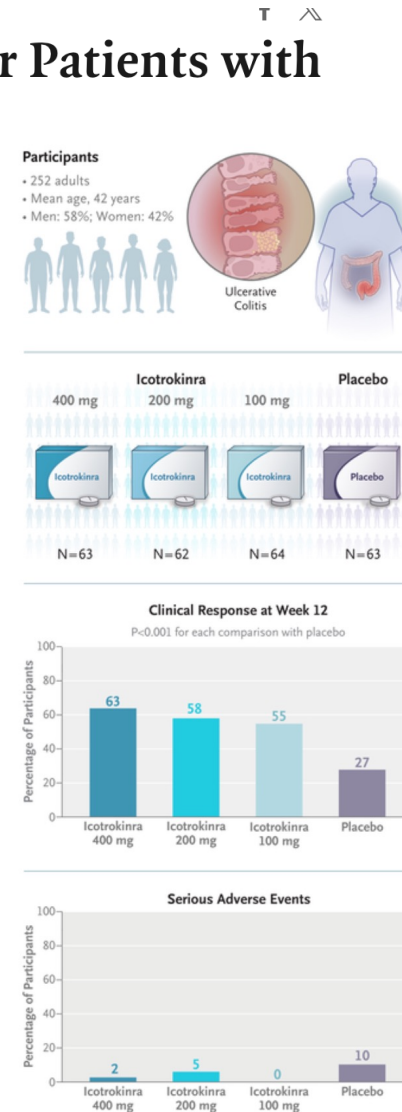
- **Entzündungsauslöser:** IL-23 treibt proentzündliche Prozesse (u. a. über den Th17-Entzündungsweg) an, die zu Schäden an der Darmschleimhaut führen.
- **Gezielte Hemmung:** Moderne Medikamente blockieren gezielt dieses Protein oder dessen Rezeptor, um die Entzündungsreaktion im Darm zu stoppen.





## Phase 2 Trial of Icotrokinra for Patients with Ulcerative Colitis

Monoclonal antibodies targeting the interleukin-23 pathway are effective in treating inflammatory bowel disease. However, these therapies must be administered intravenously or by subcutaneous injection. We conducted a phase 2b, double-blind, randomized trial of **oral icotrokinra**, a peptide that blocks the interleukin-23 receptor, in adults with moderately to severely active ulcerative colitis. Participants were assigned to receive icotrokinra at a once-daily dose of 400 mg, 200 mg, or 100 mg or placebo. The primary end point was clinical response at week 12. Secondary **end points included clinical remission, remission of symptoms, and endoscopic improvement at week 12.**



Ulcerative colitis is a chronic, immune-mediated inflammatory bowel disease with symptoms of diarrhea, rectal bleeding, abdominal pain, and bowel urgency and is associated with substantial impairment in quality of life. Approved treatments for moderately to severely active ulcerative colitis include biologic and small-molecule therapies. Inhibition of the interleukin-23 pathway is an effective, safe, and validated approach for the treatment of inflammatory bowel disease. Icotrokinra (JNJ-77242113) is a first-in-class targeted oral peptide that precisely blocks the interleukin-23 receptor. The development of oral peptide therapeutics has historically been limited by poor epithelial membrane permeability, susceptibility to enzymatic degradation in the gastrointestinal tract, and low intestinal absorption.<sup>2</sup> The cyclic peptide technology used in icotrokinra enables high stability and epithelial permeability.

## **Participants**

Eligible participants were 18 years of age or older with a diagnosis of ulcerative colitis at least 12 weeks before screening (documented by endoscopy and histologic findings) and had moderately to severely active disease, defined as a modified Mayo score of at least 5 at baseline and a Mayo endoscopic subscore of at least 2. In addition, participants had to have a history of glucocorticoid dependence; a history of unacceptable side effects with or an inadequate response to oral glucocorticoids, azathioprine, or mercaptopurine; or a history of unacceptable side effects with or an inadequate response to at least one approved advanced therapy for ulcerative colitis at an approved dose.

Participants were instructed to take icotrokinra or placebo at approximately the same time every day. For other permitted medications for ulcerative colitis that were in use at baseline (i.e., oral glucocorticoids, oral aminosalicylates, azathioprine, mercaptopurine, and methotrexate), doses were to remain stable through week 28, except for oral glucocorticoids, for which the dose was to be tapered from a maximum of 20 mg daily of a prednisone equivalent (or a maximum of 9 mg daily of budesonide or 5 mg daily of beclomethasone dipropionate) beginning at week 12.

## **End Points**

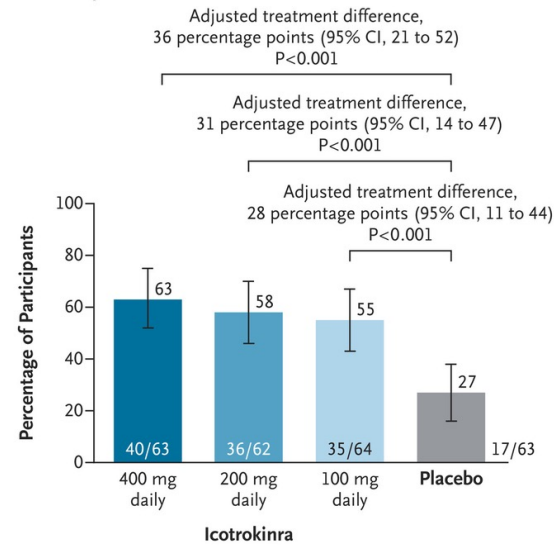
The primary end point was clinical response at week 12. Prespecified secondary end points included clinical remission and remission of symptoms.

| Characteristic                                                                                           | Icotoxinra,<br>400 mg<br>(N = 63) | Icotoxinra,<br>200 mg<br>(N = 62) | Icotoxinra,<br>100 mg<br>(N = 64) | Placebo<br>(N = 63)      | Total<br>(N = 252)       |
|----------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|--------------------------|--------------------------|
| Age — yr                                                                                                 | 40.6±14.8                         | 41.8±14.6                         | 45.8±14.6                         | 38.3±13.8                | 41.6±14.7                |
| Male sex — no. (%)                                                                                       | 40 (63)                           | 32 (52)                           | 40 (62)                           | 35 (56)                  | 147 (58)                 |
| Weight — kg                                                                                              | 71.5±18.0                         | 75.5±18.6                         | 74.6±17.7                         | 70.7±17.1                | 73.1±17.8                |
| Body-mass index†                                                                                         | 24.8±5.0                          | 26.0±5.8                          | 26.1±5.4                          | 24.4±4.9                 | 25.3±5.3                 |
| Duration of ulcerative colitis — yr                                                                      | 7.6±7.6                           | 7.8±7.5                           | 7.4±6.1                           | 8.3±8.1                  | 7.8±7.3                  |
| Extent of ulcerative colitis on screening<br>endoscopy — no. (%)                                         |                                   |                                   |                                   |                          |                          |
| Extensive disease: pancolitis                                                                            | 29 (46)                           | 23 (37)                           | 23 (36)                           | 27 (43)                  | 102 (40)                 |
| Limited to left side of colon                                                                            | 34 (54)                           | 39 (63)                           | 41 (64)                           | 36 (57)                  | 150 (60)                 |
| Modified Mayo score‡                                                                                     | 6.5±1.4                           | 6.8±1.4                           | 6.6±1.3                           | 6.8±1.2                  | 6.6±1.3                  |
| Mayo endoscopic subscore — no. (%)                                                                       |                                   |                                   |                                   |                          |                          |
| 2: Moderate                                                                                              | 26 (41)                           | 25 (40)                           | 26 (41)                           | 27 (43)                  | 104 (41)                 |
| 3: Severe                                                                                                | 37 (59)                           | 37 (60)                           | 38 (59)                           | 36 (57)                  | 148 (59)                 |
| Fecal calprotectin level                                                                                 |                                   |                                   |                                   |                          |                          |
| Median (IQR) — mg/kg§                                                                                    | 1421.3<br>(584.6–4978.6)          | 2467.0<br>(646.4–4599.6)          | 1433.3<br>(698.0–3121.2)          | 1467.0<br>(420.5–3622.0) | 1523.0<br>(587.0–3816.7) |
| >250.0 mg/kg — no./total no. (%)                                                                         | 52/58 (90)                        | 49/53 (92)                        | 47/54 (87)                        | 46/52 (88)               | 194/217 (89)             |
| C-reactive protein level                                                                                 |                                   |                                   |                                   |                          |                          |
| Median (IQR) — mg/liter¶                                                                                 | 4.0 (1.5–8.1)                     | 5.3 (1.5–11.3)                    | 3.0 (1.1–6.7)                     | 3.0 (0.9–7.0)            | 3.6 (1.3–8.1)            |
| >3.0 mg/liter — no./total no. (%)                                                                        | 33/62 (53)                        | 38/62 (61)                        | 31/63 (49)                        | 30/63 (48)               | 132/250 (53)             |
| Medication use at baseline — no. (%)                                                                     |                                   |                                   |                                   |                          |                          |
| Oral glucocorticoids                                                                                     | 23 (37)                           | 29 (47)                           | 21 (33)                           | 21 (33)                  | 94 (37)                  |
| Mercaptopurine, azathioprine, or both                                                                    | 6 (10)                            | 9 (15)                            | 9 (14)                            | 16 (25)                  | 40 (16)                  |
| Methotrexate                                                                                             | 0                                 | 1 (2)                             | 1 (2)                             | 0                        | 2 (1)                    |
| Oral 5-aminosalicylic acids                                                                              | 45 (71)                           | 42 (68)                           | 48 (75)                           | 46 (73)                  | 181 (72)                 |
| History of unacceptable side effects with or<br>inadequate response to advanced<br>therapies             |                                   |                                   |                                   |                          |                          |
| No — no. (%)                                                                                             | 34 (54)                           | 36 (58)                           | 38 (59)                           | 35 (56)                  | 143 (57)                 |
| No previous exposure to advanced<br>therapies — no./total no. (%)                                        | 31/34 (91)                        | 31/36 (86)                        | 34/38 (89)                        | 32/35 (91)               | 128/143 (90)             |
| Previous exposure to advanced thera-<br>pies without documented treatment<br>failure — no./total no. (%) | 3/34 (9)                          | 5/36 (14)                         | 4/38 (11)                         | 3/35 (9)                 | 15/143 (10)              |
| Yes — no. (%)                                                                                            | 29 (46)                           | 26 (42)                           | 26 (41)                           | 28 (44)                  | 109 (43)                 |
| 1 Class or mechanism of action —<br>no./total no. (%)                                                    | 15/29 (52)                        | 21/26 (81)                        | 19/26 (73)                        | 22/28 (79)               | 77/109 (71)              |
| 2 Classes or mechanisms of action —<br>no./total no. (%)                                                 | 14/29 (48)                        | 5/26 (19)                         | 6/26 (23)                         | 6/28 (21)                | 31/109 (28)              |
| >2 Classes or mechanisms of action —<br>no./total no. (%)                                                | 0                                 | 0                                 | 1/26 (4)                          | 0                        | 1/109 (1)                |

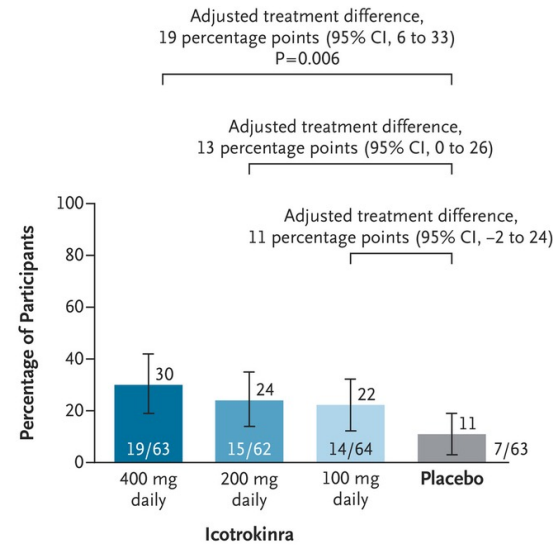
## Adverse Events through Week 28.

| Characteristic or Event                                                         | Icotoxinra,<br>400 mg<br>(N = 63) | Icotoxinra,<br>200 mg<br>(N = 62) | Icotoxinra,<br>100 mg<br>(N = 64) | Placebo<br>(N = 63)†   | Rescue Therapy for<br>Nonresponse in<br>Placebo Group<br>(N = 23)‡ |
|---------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|------------------------|--------------------------------------------------------------------|
| Average duration of follow-up — wk                                              | 26.0                              | 26.1                              | 26.6                              | 20.3                   | 11.8                                                               |
| Average duration of treatment period — wk                                       | 25.2                              | 25.4                              | 26.1                              | 19.6                   | 11.6                                                               |
| Total participant-yr of follow-up                                               | 31.4                              | 31.0                              | 32.6                              | 24.6                   | 5.2                                                                |
| Any adverse event — no. (%)                                                     | 38 (60)                           | 41 (66)                           | 42 (66)                           | 39 (62)                | 6 (26)                                                             |
| Serious adverse event — no. (%)                                                 | 1 (2)                             | 3 (5)                             | 0                                 | 6 (10)                 | 0                                                                  |
| Adverse event leading to discontinuation of<br>trial regimen — no. (%)          | 2 (3)                             | 4 (6)                             | 0                                 | 7 (11)                 | 0                                                                  |
| Infection — no. (%)§                                                            | 15 (24)                           | 24 (39)                           | 18 (28)                           | 17 (27)                | 2 (9)                                                              |
| Serious infection — no. (%)§                                                    | 0                                 | 0                                 | 0                                 | 1 (2)                  | 0                                                                  |
| Death — no. (%)                                                                 | 0                                 | 0                                 | 0                                 | 0                      | 0                                                                  |
| Events per 100 participant-yr of follow-up<br>(95% CI)¶                         |                                   |                                   |                                   |                        |                                                                    |
| Adverse events                                                                  | 280.3<br>(224.8–345.3)            | 371.0<br>(306.3–445.3)            | 300.6<br>(244.1–366.4)            | 386.2<br>(312.4–472.1) | 230.8<br>(119.2–403.1)                                             |
| Serious adverse events                                                          | 6.4<br>(0.8–23.0)                 | 9.7<br>(2.0–28.3)                 | 0<br>(0.0–9.2)                    | 28.5<br>(11.4–58.6)    | 0<br>(0.0–57.6)                                                    |
| Adverse events leading to discontinuation<br>of trial regimen                   | 6.4<br>(0.8–23.0)                 | 19.4<br>(7.1–42.1)                | 0<br>(0.0–9.2)                    | 32.5<br>(14.0–64.1)    | 0<br>(0.0–57.6)                                                    |
| Infections§                                                                     | 57.3<br>(34.0–90.6)               | 103.2<br>(70.6–145.7)             | 70.6<br>(44.7–105.9)              | 97.6<br>(62.5–145.2)   | 38.5<br>(4.7–138.9)                                                |
| Adverse events occurring in ≥5% of the par-<br>ticipants in any group — no. (%) |                                   |                                   |                                   |                        |                                                                    |
| Worsening of ulcerative colitis                                                 | 5 (8)                             | 9 (15)                            | 4 (6)                             | 8 (13)                 | 1 (4)                                                              |
| Upper respiratory tract infection                                               | 6 (10)                            | 4 (6)                             | 8 (12)                            | 1 (2)                  | 1 (4)                                                              |
| Nasopharyngitis                                                                 | 6 (10)                            | 4 (6)                             | 5 (8)                             | 4 (6)                  | 0                                                                  |
| Headache                                                                        | 4 (6)                             | 3 (5)                             | 6 (9)                             | 1 (2)                  | 1 (4)                                                              |
| Arthralgia                                                                      | 2 (3)                             | 4 (6)                             | 3 (5)                             | 2 (3)                  | 0                                                                  |
| Abdominal pain                                                                  | 1 (2)                             | 4 (6)                             | 2 (3)                             | 2 (3)                  | 0                                                                  |
| Influenza                                                                       | 1 (2)                             | 4 (6)                             | 1 (2)                             | 2 (3)                  | 1 (4)                                                              |
| Anemia                                                                          | 2 (3)                             | 1 (2)                             | 1 (2)                             | 4 (6)                  | 0                                                                  |
| Covid-19                                                                        | 0                                 | 4 (6)                             | 0                                 | 1 (2)                  | 0                                                                  |

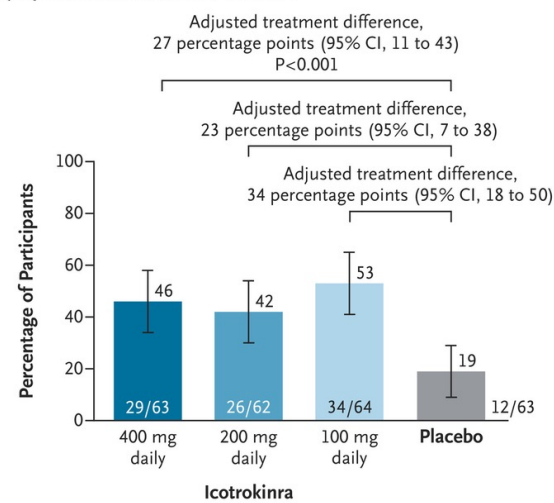
### A Clinical Response at Week 12



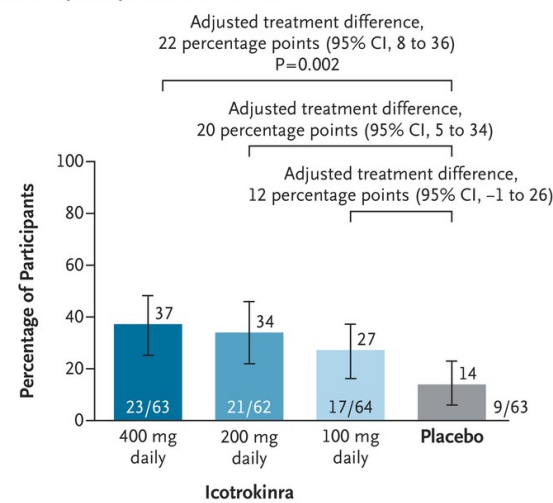
### B Clinical Remission at Week 12



### C Symptomatic Remission at Week 12



### D Endoscopic Improvement at Week 12



### Primary and Secondary End Points at Week 12.

Shown are the percentages of participants with a clinical response at week 12 (Panel A, primary end point) and the percentages of participants with clinical remission (Panel B), symptomatic remission (Panel C), and endoscopic improvement (Panel D) at week 12 (secondary end points). Adjusted treatment differences and 95% confidence intervals are presented without P values for comparisons after the last significant P value in the fixed-sequence testing procedure. Clinical response was defined as a decrease from baseline in the modified Mayo score by at least 30% and at least 2 points, with either a decrease of at least 1 point from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. Modified Mayo scores for ulcerative colitis range from 0 to 9 and include subscores for rectal bleeding, stool frequency, and endoscopic findings, each with a range of 0 to 3, with higher scores indicating greater severity. Clinical remission was defined by a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopic subscore of 0 or 1. Symptomatic remission was defined by a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, and endoscopic improvement was defined by an endoscopic subscore of 0 or 1. I bars indicate 95% confidence intervals.





### Ulcerative Colitis

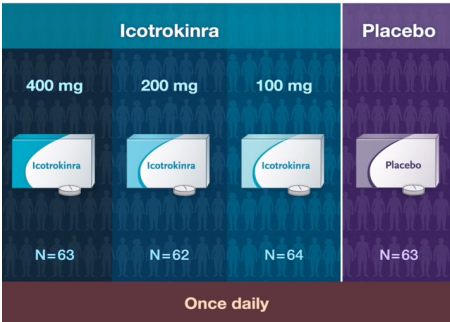
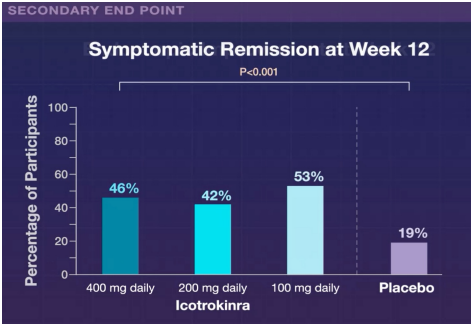
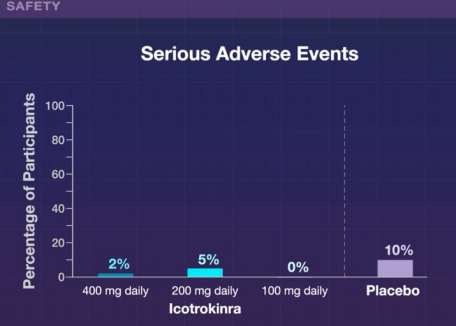
Chronic, immune-mediated inflammatory bowel disease

Symptoms include:

- Diarrhea
- Rectal bleeding
- Abdominal pain
- Bowel urgency



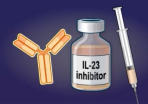
**Substantial impairment in quality of life**





### Monoclonal antibodies

that target interleukin-23 (IL-23) pathway:

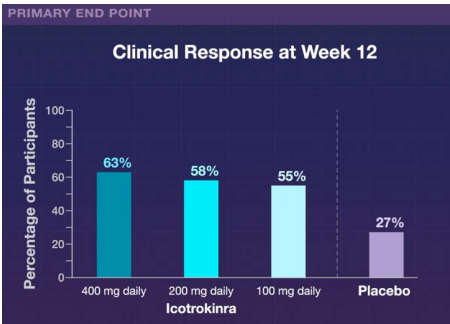
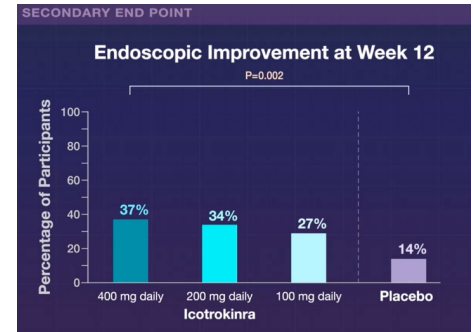
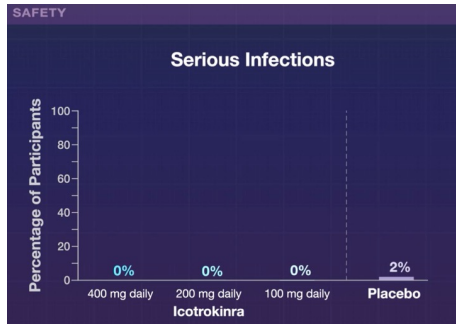




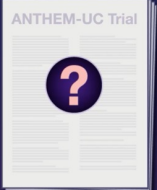
Effective for inflammatory bowel disease



Require intravenous or subcutaneous administration



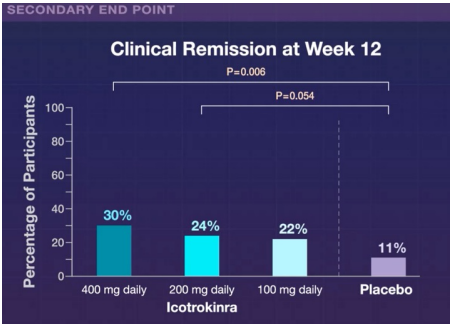
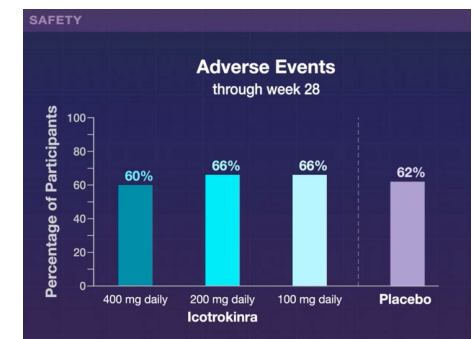
SAFETY AND EFFICACY



Icotrokinra

First-in-class, targeted oral peptide







### Moderately to severely active ulcerative colitis

Once-daily oral icotrokinra

Icotrokinra

400 mg

Icotrokinra

200 mg

Icotrokinra

100 mg



**Significantly improved clinical response at week 12**

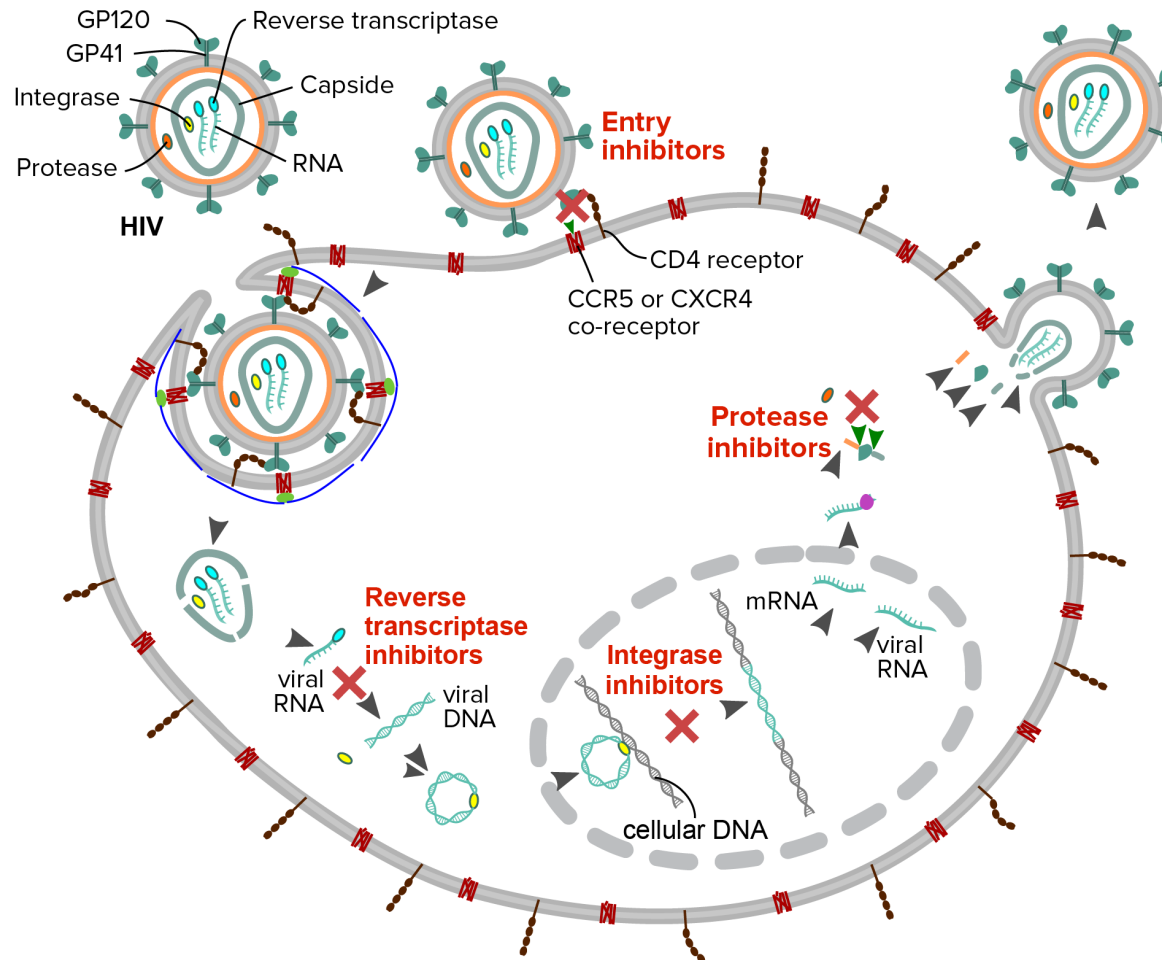


**Cabotegravir ist ein antiretroviraler Arzneistoff** aus der Gruppe der HIV-Integrase-Hemmer (INSTI). Er wird zur Behandlung und zur Prävention (PrEP) einer HIV-1-Infektion eingesetzt.

### **Anwendungsgebiete:**

- **HIV-1-Therapie:** Zur Behandlung von Erwachsenen und Jugendlichen (ab 12 Jahren, Mindestgewicht 35 kg), die bereits virologisch unterdrückt sind, in Kombination mit Rilpivirin.
- **PrEP (Prä-Expositions-Prophylaxe):** Zum Schutz vor einer HIV-1-Infektion bei Personen mit einem Risiko für eine Ansteckung.
- **Darreichungsformen:** Es gibt ihn als Filmtabletten zur oralen Einnahme sowie als intramuskuläre Depot-Injektion (gesäßmuskulär), die in der Regel alle 1 bis 2 Monate verabreicht wird. Eine frühere Pflicht zur oralen Einleitungsphase (Oral Lead-in) wurde weitgehend angepasst oder ist optional.
- **Wirkungsweise:** Cabotegravir blockiert das virale Enzym Integrase. Dadurch kann das Erbgut des HI-Virus nicht in die menschliche Wirtszelle eingebaut werden.

# Anti-AIDS Drugs



- **Standard-Oraltherapie (SoC):** ca. 50.668 \$ pro Jahr
- **Cabotegravir/Rilpivirin-Injektion (LA):** ca. 67.041 \$ im ersten Jahr

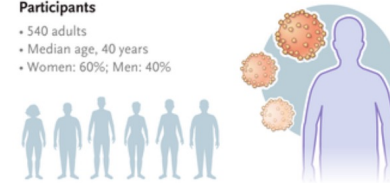
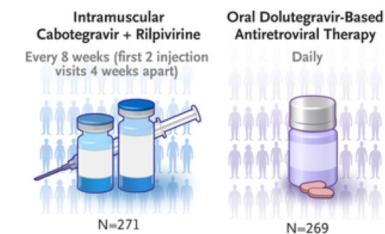
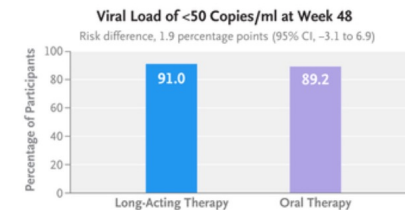
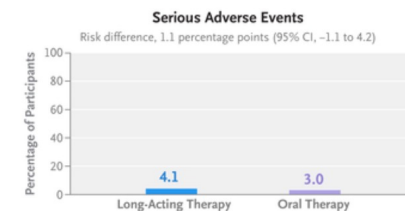
**Klinischer Nutzen:** Trotz der höheren Anschaffungskosten gilt diese Option als hochgradig kosteneffektiv. Sie steigert die Rate der Virusunterdrückung (Suppression) in dieser Gruppe dramatisch von **15 % auf 92 %**

# Long-Acting HIV Therapy in African Adults with Adherence Challenges

In eastern and southern Africa, approximately 1 million people living with human immunodeficiency virus (HIV) and receiving oral therapy do not have viral suppression because of adherence challenges. We conducted a phase 3b, open-label, randomized trial to compare long-acting injectable cabotegravir plus rilpivirine with oral dolutegravir-based therapy among adults with virally suppressed HIV type 1 (viral load, <200 copies per milliliter) and suboptimal adherence or care engagement. The participants were assigned in a 1:1 ratio to receive intramuscular injections of cabotegravir (600 mg) plus rilpivirine (900 mg) every 8 weeks, with the first two injection visits occurring 4 weeks apart, or to continue daily oral dolutegravir-based therapy; baseline drug-resistance testing was not performed. The primary end point was a viral load of less than 50 copies per milliliter at week 48; noninferiority was assessed with a margin of –10 percentage points. Confirmed virologic failure (two consecutive viral loads of  $\geq 200$  copies per milliliter) was a key secondary end point.

## Participants

- 540 adults
- Median age, 40 years
- Women: 60%; Men: 40%



Long-acting injectable antiretroviral agents represent a paradigm shift in both the prevention and the management of human immunodeficiency virus (HIV) infection, with the potential to curb the epidemic if implemented successfully in the highest-burden setting, sub-Saharan Africa.

Approximately two thirds of the world population living with HIV reside in this region, in which approximately 390,000 acquired immunodeficiency syndrome (AIDS)–related deaths and 640,000 new transmissions continue to occur annually, despite the widespread availability of highly effective oral antiretroviral therapy. AIDS-related illnesses occur in persons who face challenges with treatment adherence, which highlights the limitations of daily oral regimens. When adherence is inconsistent, the risk of death is two to four times as high as the risk when therapy is taken consistently, and spikes in viremia that occur as people oscillate between taking and not taking oral antiretroviral therapy contribute increasingly to transmission. Treatment innovations that close the adherence gap are critical to expediting and sustaining epidemic control.

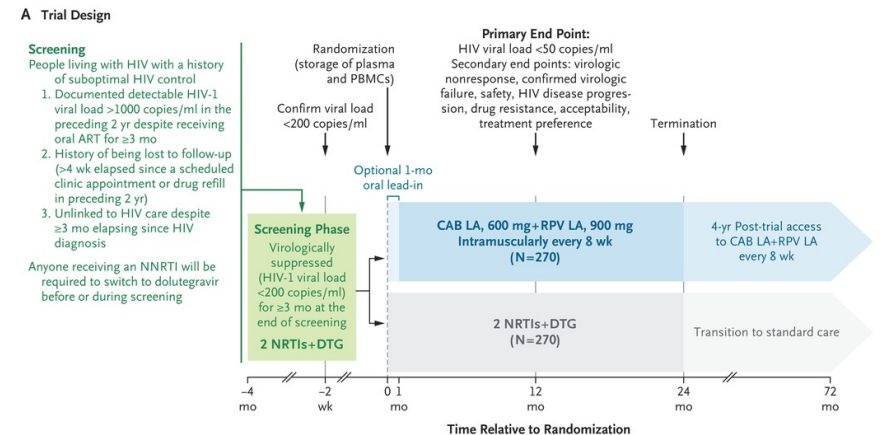
## Methods

### Trial Design and Oversight

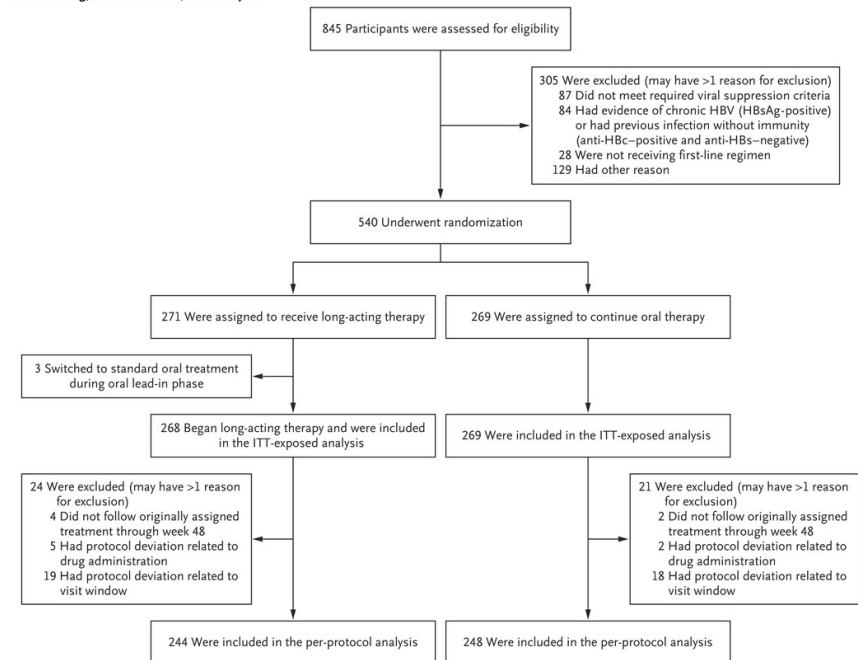
We conducted a phase 3b, open-label, randomized, noninferiority trial — the Improving HIV-1 Outcomes in Africa with Long-Acting Antiretrovirals (IMPALA) trial — to evaluate the efficacy of switching therapy to long-acting cabotegravir plus rilpivirine administered intramuscularly every 8 weeks, with the first two injection visits occurring 4 weeks apart, from daily oral antiretroviral therapy among adults with virologically suppressed HIV who had recent challenges in maintaining adherence to daily oral therapy or engagement in care.

### Assessments and End Points

The primary end point was a viral load of less than 50 copies per milliliter at 48 weeks.



### B Screening, Randomization, and Analysis



| Characteristic                                                | Long-Acting Therapy<br>(N = 271) | Oral Therapy<br>(N = 269) | Total<br>(N = 540)  |
|---------------------------------------------------------------|----------------------------------|---------------------------|---------------------|
| Median age (IQR) — yr                                         | 40.0 (33.0–48.0)                 | 40.0 (33.0–48.0)          | 40.0 (33.0–48.0)    |
| Age group — no. (%)                                           |                                  |                           |                     |
| 19 to 24 yr                                                   | 15 (5.5)                         | 15 (5.6)                  | 30 (5.6)            |
| 25 to 34 yr                                                   | 66 (24.4)                        | 61 (22.7)                 | 127 (23.5)          |
| 35 to 50 yr                                                   | 131 (48.3)                       | 135 (50.2)                | 266 (49.3)          |
| >50 yr                                                        | 59 (21.8)                        | 58 (21.6)                 | 117 (21.7)          |
| Sex — no. (%)†                                                |                                  |                           |                     |
| Female                                                        | 169 (62.4)                       | 155 (57.6)                | 324 (60.0)          |
| Male                                                          | 102 (37.6)                       | 114 (42.4)                | 216 (40.0)          |
| Country of residence — no. (%)                                |                                  |                           |                     |
| Kenya                                                         | 81 (29.9)                        | 79 (29.4)                 | 160 (29.6)          |
| South Africa                                                  | 70 (25.8)                        | 70 (26.0)                 | 140 (25.9)          |
| Uganda                                                        | 120 (44.3)                       | 120 (44.6)                | 240 (44.4)          |
| Black race — no. (%)                                          | 271 (100)                        | 267 (99.3)                | 538 (99.6)          |
| Employment status — no. (%)                                   |                                  |                           |                     |
| Formal employment                                             | 58 (21.4)                        | 38 (14.1)                 | 96 (17.8)           |
| Self-employed                                                 | 82 (30.3)                        | 107 (39.8)                | 189 (35.0)          |
| Casual laborer                                                | 60 (22.1)                        | 56 (20.8)                 | 116 (21.5)          |
| Unemployed                                                    | 71 (26.2)                        | 68 (25.3)                 | 139 (25.7)          |
| CD4 T-cell count                                              |                                  |                           |                     |
| Median (IQR) — cells/mm <sup>3</sup>                          | 647.0 (447.0–833.5)              | 617.0 (461.0–896.0)       | 628.5 (453.0–872.5) |
| <200 cells/mm <sup>3</sup>                                    | 11 (4.1)                         | 14 (5.2)                  | 25 (4.6)            |
| Hepatitis B status at trial entry — no. (%)‡                  |                                  |                           |                     |
| Anti-HBc–negative, anti-HBs–negative                          | 165 (60.9)                       | 165 (61.3)                | 330 (61.1)          |
| Anti-HBc–negative, anti-HBs–positive                          | 20 (7.4)                         | 22 (8.2)                  | 42 (7.8)            |
| Anti-HBc–positive, anti-HBs–positive                          | 86 (31.7)                        | 81 (30.1)                 | 167 (30.9)          |
| Baseline BMI§                                                 |                                  |                           |                     |
| Median (IQR)                                                  | 24.4 (21.7–30.1)                 | 24.5 (21.3–28.5)          | 24.5 (21.5–29.2)    |
| ≥30 — no. (%)                                                 | 69 (25.5)                        | 51 (19.0)                 | 120 (22.2)          |
| Viral subtype — no./total no. (%)¶                            |                                  |                           |                     |
| A1                                                            | 82/174 (47.1)                    | 91/169 (53.8)             | 173/343 (50.4)      |
| C                                                             | 33/174 (19.0)                    | 31/169 (18.3)             | 64/343 (18.7)       |
| Other                                                         | 59/174 (33.9)                    | 47/169 (27.8)             | 106/343 (30.9)      |
| Resistance mutations — no./total no. (%)                      |                                  |                           |                     |
| Rilpivirine RAMs                                              | 8/162 (4.9)                      | 10/151 (6.6)              | 18/313 (5.8)        |
| Predicted intermediate- or high-level rilpivirine resistance  | 5/162 (3.1)                      | 2/151 (1.3)               | 7/313 (2.2)         |
| Cabotegravir RAMs                                             | 1/172 (0.6)                      | 0/167                     | 1/339 (0.3)         |
| Predicted intermediate- or high-level cabotegravir resistance | 1/172 (0.6)                      | 0/167                     | 1/339 (0.3)         |
| Median duration of HIV treatment (IQR) — yr                   | 7.5 (4.8–11.0)                   | 7.41 (4.5–10.8)           | 7.5 (4.6–10.8)      |
| Previous NNRTI exposure — no. (%)                             | 217 (80.1)                       | 207 (77.0)                | 424 (78.5)          |
| Previous AIDS-defining illness — no. (%)                      | 69 (25.5)                        | 73 (27.1)                 | 142 (26.3)          |
| Receiving INSTI-based regimen at screening — no. (%)          | 270 (99.6)                       | 269 (100)                 | 539 (99.8)          |

## Participants with Confirmed Virologic Failure by Week 48 in the Long-Acting Therapy Group.

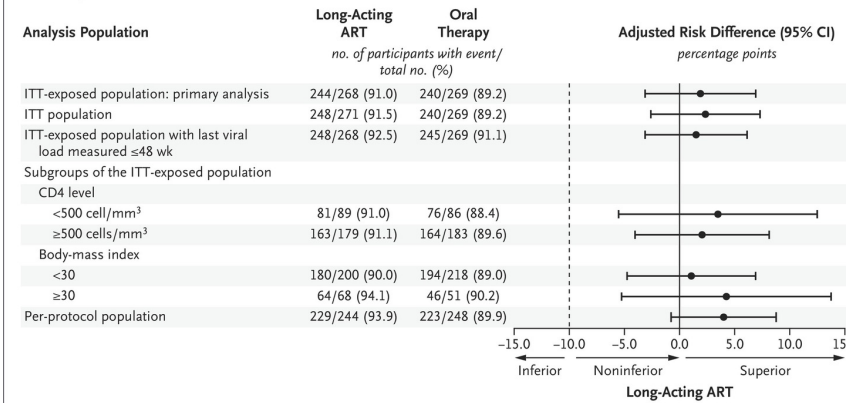
| Characteristic                                     | Participant 1                         | Participant 2                                                                            | Participant 3                                                                            | Participant 4                                                                   | Participant 5                                                                   |
|----------------------------------------------------|---------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| HIV subtype                                        | A1                                    | C                                                                                        | A1                                                                                       | C                                                                               | A1                                                                              |
| Visit with documented failure                      | Month 6                               | Month 8                                                                                  | Month 12                                                                                 | Month 12                                                                        | Month 12                                                                        |
| Baseline resistance†                               | NNRTI: did not amplify<br>INSTI: none | NNRTI: did not amplify<br>INSTI: none                                                    | NNRTI: K103S<br>INSTI: none                                                              | NNRTI: L100I, K103N<br>INSTI: L74I<br>High-level rilpivirine resistance         | NNRTI: did not amplify<br>INSTI: none                                           |
| HIV viral load at failure — copies/ml              | 3336                                  | 6303                                                                                     | 36,670                                                                                   | 475                                                                             | 5232                                                                            |
| Repeat HIV viral load — copies/ml                  | 1809                                  | 1888                                                                                     | 96,120                                                                                   | 282                                                                             | 231                                                                             |
| NNRTI RAMs at failure                              | Insufficient volume                   | E138K, Y188L                                                                             | K103S, E138K, Y181C                                                                      | K103N, V108I                                                                    | E138K, Y181C                                                                    |
| NNRTI resistance prediction                        | NA                                    | Low: etravirine<br>High: efavirenz, nevirapine, rilpivirine                              | Intermediate: etravirine<br>High: rilpivirine, efavirenz, nevirapine                     | Sensitive: rilpivirine<br>High: efavirenz, nevirapine                           | Intermediate: efavirenz, etravirine<br>High: rilpivirine, nevirapine            |
| INSTI RAMs at failure                              | Insufficient volume                   | E138K, Q148R                                                                             | E138K, Q148R                                                                             | Q148R                                                                           | Q148R                                                                           |
| INSTI resistance prediction‡                       | NA                                    | Intermediate: dolutegravir, bictegravir<br>High: cabotegravir, raltegravir, elvitegravir | Intermediate: dolutegravir, bictegravir<br>High: cabotegravir, raltegravir, elvitegravir | Low: dolutegravir, bictegravir<br>High: cabotegravir, raltegravir, elvitegravir | Low: dolutegravir, bictegravir<br>High: cabotegravir, raltegravir, elvitegravir |
| Identifiable risk factors or drug–drug interaction | Herbal medicine                       | BMI, 38.3                                                                                | None                                                                                     | Rilpivirine RAMs (L100I with K103N)                                             | None                                                                            |
| Current regimen                                    | Tenofovir, lamivudine, dolutegravir   | Tenofovir, lamivudine, dolutegravir                                                      | Tenofovir, lamivudine, dolutegravir                                                      | Tenofovir, lamivudine, emtricitabine + ritonavir-boosted lopinavir              | Tenofovir, lamivudine, dolutegravir                                             |
| Most recent HIV viral load — copies/ml§            | <50                                   | <50                                                                                      | <50                                                                                      | <50                                                                             | <50                                                                             |



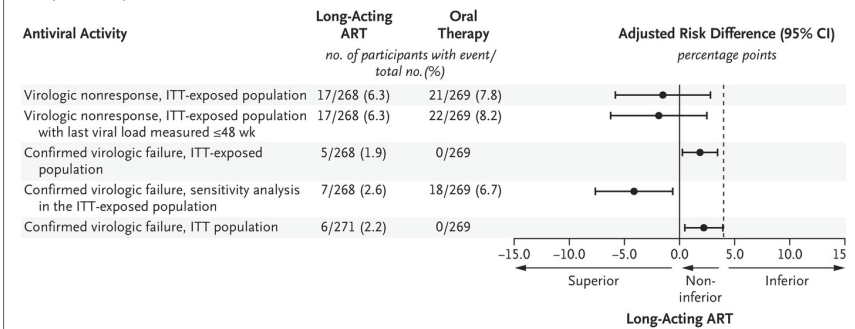
## Adverse Events

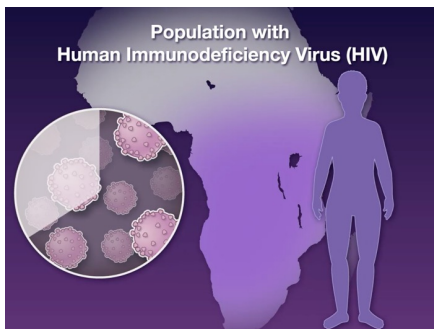
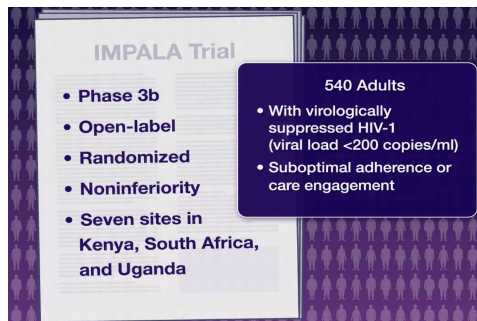
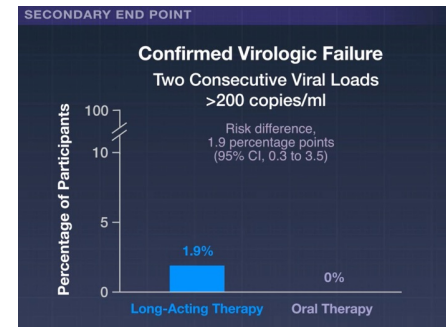
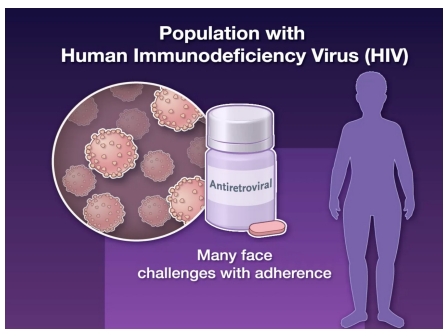
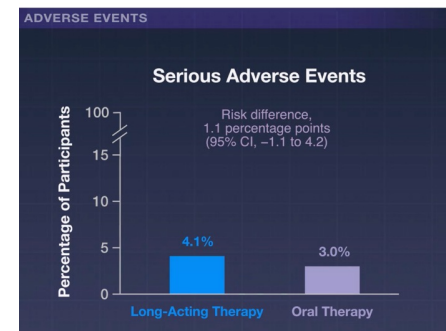
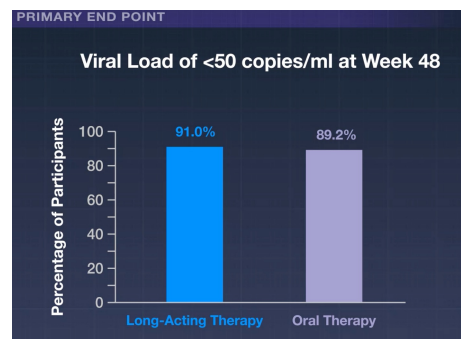
| Event                                                                                     | Long-Acting Therapy<br>(N=271) | Oral Therapy<br>(N=269) | Adjusted Risk<br>Difference<br>(95% CI) <sup>†</sup> |
|-------------------------------------------------------------------------------------------|--------------------------------|-------------------------|------------------------------------------------------|
|                                                                                           |                                |                         | percentage points                                    |
| Adverse event of grade 1 to 4                                                             |                                |                         |                                                      |
| Any adverse event, excluding injection-site reaction — no. (%)                            | 228 (84.1)                     | 206 (76.6)              | 7.6 (3.1 to 13.7)                                    |
| Laboratory abnormality — no. (%)                                                          | 143 (52.8)                     | 148 (55.0)              |                                                      |
| Drug-related adverse event, excluding injection-site reaction — no. (%) <sup>‡</sup>      | 48 (17.7)                      | 36 (13.4)               |                                                      |
| Adverse event leading to drug discontinuation — no. (%) <sup>§</sup>                      | 7 (2.6)                        | 3 (1.1)                 |                                                      |
| Drug-related adverse event leading to drug discontinuation — no. (%) <sup>¶</sup>         | 2 (0.7)                        | 2 (0.7)                 |                                                      |
| No. of events/no. of visits (rate per visit) <sup>  </sup>                                | 719/2436 (0.30)                | 575/1571 (0.37)         |                                                      |
| Any adverse event of grade ≥3 — no. (%)                                                   | 33 (12.2)                      | 24 (8.9)                | 3.3 (–1.8 to 8.3)                                    |
| Drug-related adverse event of grade ≥3, excluding injection-site reaction <sup>**</sup>   | 1 (0.4)                        | 2 (0.7)                 |                                                      |
| Any serious adverse event                                                                 | 11 (4.1)                       | 8 (3.0)                 | 1.1 (–1.1 to 4.2)                                    |
| Injection site reaction — no. (%)                                                         |                                |                         |                                                      |
| Grade 1 or 2                                                                              | 101 (37.3)                     | NA                      |                                                      |
| Grade ≥3                                                                                  | 0                              | NA                      |                                                      |
| Top five clinical events, excluding injection-site reaction, across both groups — no. (%) |                                |                         |                                                      |
| Upper respiratory tract infection                                                         | 51 (18.8)                      | 38 (14.1)               |                                                      |
| Rash                                                                                      | 27 (10.0)                      | 15 (5.6)                |                                                      |
| Urinary tract infection                                                                   | 18 (6.6)                       | 18 (6.7)                |                                                      |
| Malaria                                                                                   | 22 (8.1)                       | 14 (5.2)                |                                                      |
| Headache                                                                                  | 18 (6.6)                       | 16 (5.9)                |                                                      |

### A Primary End Point



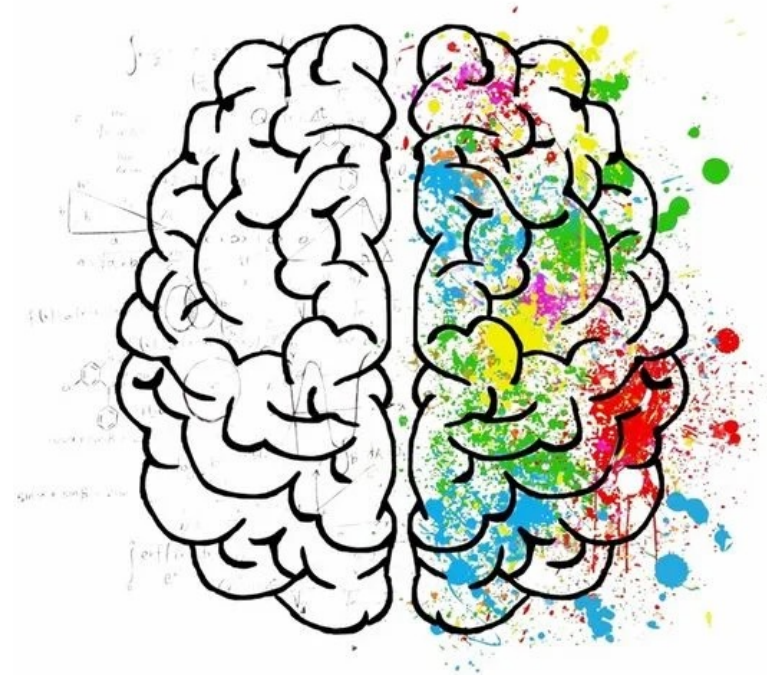
### B Key Secondary End Points







## Leben mit **ADHS**



ADHS verstehen lernen für  
Erwachsene, **Kinder** und Eltern

von Patrick Sánchez Beyrer

# Adult Attention Deficit–Hyperactivity Disorder

## Summary

Attention deficit–hyperactivity disorder (ADHD) is a medical condition that is present in approximately 2.5% of adults worldwide and manifests in a variety of different ways across the lifespan. Adults with ADHD often have coexisting psychiatric disorders such as anxiety, mood, sleep, substance use, and personality disorders and are at increased risk for coexisting somatic conditions such as obesity, cardiovascular and cerebrovascular disease, type 1 and type 2 diabetes, and immune and inflammatory conditions. Hence, such adults may be seen by clinicians providing care for a wide range of psychiatric and somatic conditions. Nevertheless, ADHD remains unrecognized and undiagnosed in many persons. Assessment requires interviewing of the patient for core ADHD symptoms, coexisting conditions, and their functional effects, which can be facilitated by using standardized rating scales. Key components of treatment are psychoeducation and psychostimulant or nonstimulant medication, mostly in combination with psychosocial interventions and lifestyle guidance.

A 38-year-old woman presents with job burnout after not having a response to earlier cognitive-behavior therapy for fear of failure at work and emotional instability. She struggles as a journalist with procrastination, failure to meet deadlines, and difficulty in finishing her writing assignments. These behaviors have not only caused substantial problems at work; her inability to manage details and stick to a schedule are also present at home and negatively affect her marriage and her ability to parent. She has difficulty sleeping and has obesity. How would you evaluate and treat this patient?

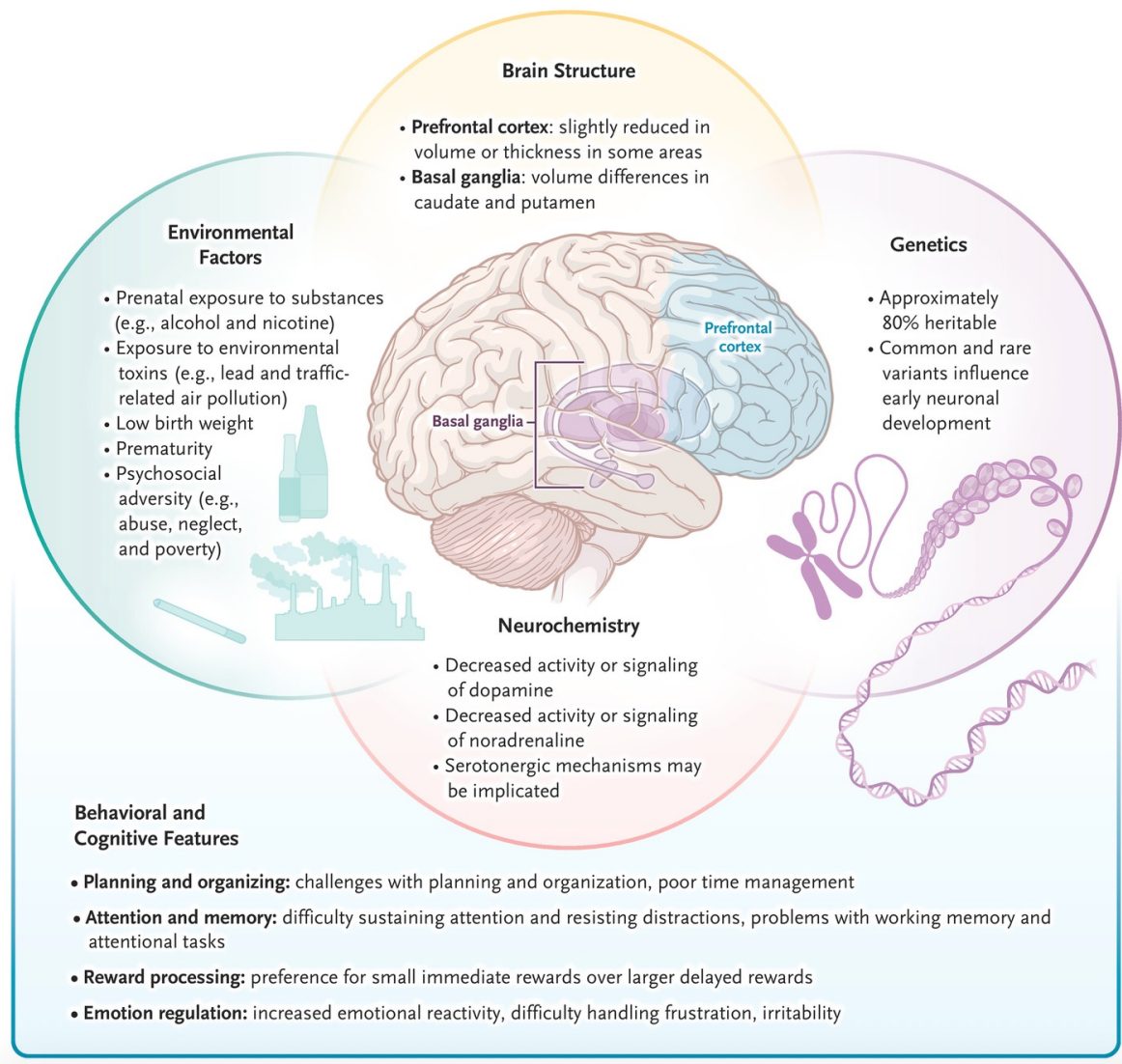
### **The Clinical Problem**

Attention deficit–hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate and impairing symptoms of inattention or hyperactivity–impulsivity. Although ADHD has long been considered to be a childhood-limited condition, numerous follow-up studies have shown a persistent course into adulthood in at least one third of cases and lasting functional impairments in an even larger proportion.

## Adult Attention Deficit–Hyperactivity Disorder (ADHD)

- ADHD is a medical condition that manifests in a variety of different ways across the lifespan.
- Adults with ADHD may be seen by clinicians providing care for a wide range of psychiatric and somatic conditions, although ADHD remains unrecognized and undiagnosed in many persons.
- Many adults with ADHD have complex psychiatric and medical histories.
- The key components of treatment are psychoeducation and psychostimulant or nonstimulant medication, mostly in combination with psychosocial interventions.





## Neurobiologic Mechanisms of Attention Deficit–Hyperactivity Disorder (ADHD).

Persons with ADHD have differences in neurotransmitters, brain circuits and structure, genetics, and environmental factors as compared with persons without ADHD. The differences affect regulation of attention, behavior, and emotions. Note that the overlap of differences in brain structure among persons is large and that these are group-level trends, not diagnostic tests.

## **Summary of DSM-5-TR Criteria for Adult Attention Deficit–Hyperactivity Disorder (ADHD).**

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### **Overall diagnostic criteria**

Five or more symptoms of inattention or five or more symptoms of hyperactivity–impulsivity in persons 17 years of age or older (the threshold is six or more symptoms in persons younger than 17 years of age)  
Several symptoms present by 12 years of age  
Several symptoms present in two or more settings  
Symptoms present for 6 months or longer  
Several interfere with or reduce quality of social, academic, or occupational functioning  
Symptoms are not better explained by another condition, such as depression or substance use disorder

### **Inattention (nine symptoms)**

Lack of attention to details or makes careless mistakes  
Difficulty sustaining attention  
Does not listen when spoken to directly  
Difficulty completing or finishing tasks or jobs  
Problems organizing tasks and activities.  
Avoids or dislikes sustained mental effort  
Loses and misplaces things  
Easily distracted  
Forgetful in daily activities

### **Hyperactivity–impulsivity (nine symptoms)**

Fidgeting (hands or feet) or squirming in seat  
Leaves seat when remaining seated is expected  
Restless or overactive  
Difficulty engaging in leisure activities quietly  
Always “on the go”  
Talks excessively  
Blurts out answers before questions have been completed  
Difficulty waiting in line or taking turns  
Interrupts or intrudes on others when they are working or busy

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## Treatments for ADHD in Adults.

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### Psychoeducation

Essential on beginning treatment; can be done by the prescriber or someone else on the team.

### Evidence-based psychosocial treatment

Cognitive-behavioral therapy targeted to ADHD involving cognitive restructuring, metacognitive therapy, organizational-skills training, and dialectical behavior therapy; can be done in individual or group setting; depends on availability of skilled provider.

Effect sizes: global functioning, 0.47; occupational functioning, 1.00; social relationships, 0.36; academic functioning, 0.48; quality of life, 0.28.<sup>20</sup>

### Stimulant medication

Methylphenidate and amphetamine classes are both approved; can start with either; often recommended as a first-choice option.

Effect sizes (core ADHD symptoms): The latest network meta-analysis in adult ADHD showed the effect size for both stimulant classes together, with no significant difference between the classes: 0.39 for patient-rated symptoms and 0.61 for clinician-rated symptoms.<sup>18</sup>

### Nonstimulant medication

Three classes of Food and Drug Administration (FDA)–approved medications are potentially available: norepinephrine-reuptake inhibitor (NRI) (atomoxetine), NRI–serotonin modulator (extended-release viloxazine), and the  $\alpha_2$  agonists (extended-release guanfacine and extended-release clonidine). A fourth class — triple reuptake inhibitor (centanafadine)<sup>†</sup> — was recently approved for children and adults by the FDA but has not yet been scheduled by the Drug Enforcement Administration. The  $\alpha_2$  agonists are FDA-approved in children and adolescents but not adults and are used on an off-label basis; bupropion is also often used off-label. Nonstimulants are often a second-choice option in most guidelines, although efficacy is similar to that of stimulants in selected persons.

Effect sizes (core ADHD symptoms): A recent meta-analysis showed a moderate effect size for atomoxetine (15 randomized, controlled trials [RCTs]; effect size, 0.48) and guanfacine (2 RCTs; effect size, 0.66). The effect size for extended-release viloxazine is in the same range but with only 1 RCT to date.<sup>21</sup> Another meta-analysis showed a modest effect size for centanafadine (5 RCTs; effect size, 0.37).<sup>22</sup>

### Other

Available evidence indicates that devices, therapeutic games, and neuromodulation lack efficacy with respect to core ADHD symptoms but may affect overall function. They are not recommended as primary treatment methods. There are few studies on the effects of diets and supplements on core symptoms in adult ADHD.

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## **Tips on Optimizing Medication Treatment.**

### **Overall**

Begin with psychoeducation.

Engage patients regarding goals of treatment and allow them to participate in treatment selection once appropriately educated.

Identify target symptoms — two or three individualized items that need to change and represent targets of treatment — across settings and time of day.

Choose an FDA-approved medication: stimulant or nonstimulant (understanding that stimulants on average offer somewhat superior response and are recommended as a first option in most guidelines).

Frequent visits on starting medication; use symptom-based scales.

Aim for excellent response (40–50% decrease in ADHD symptoms) and good-to-excellent treatment acceptability.

Improvement in target symptoms is essential.

Monitor for adverse events, treatment acceptability, and adherence; be alert to any indications of misuse or diversion of medication.

Monitor for substance use.

Consider addition of evidence-based psychosocial treatment either at the outset or if there are residual symptoms or problems with organization or executive functions despite medication.

### **Stimulants**

Determine what times of the day need to be covered.

Begin with a long-acting stimulant formulation in either class.

Consider alternative formulations or addition of immediate-release stimulant if duration is not optimal; usually, this is known quickly.

Make sure to test higher doses because it is not always apparent what the optimal response is.

Switch to the other stimulant class if response or treatment acceptability is not optimal.

Consider switching to or adding a nonstimulant for patients with a partial response or those with side effects at needed doses.

### **Nonstimulants**

Begin with an FDA-approved medication (NRI or NRI–serotonin modulator, or triple reuptake inhibitor).

Determine desired target dose with the use of weight-based calculations if indicated.

Increase dose to the expected range before deciding whether the medication is effective.

Determine whether there is at least an entry level response by 2–4 weeks.

Consider switching to or adding another nonstimulant or a stimulant if there is inadequate response or acceptability.

Consider using non-FDA-approved medications with demonstrated efficacy (e.g.,  $\alpha_2$  or bupropion) if there is inadequate response or acceptability with FDA-approved medications or if there are coexisting conditions.

### Professional Guidelines for Assessment and Treatment of Adult ADHD.

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United Kingdom: National Institute for Clinical Care and Excellence  
(<https://www.nice.org.uk/guidance/ng87>)

Canada: Canadian ADHD Resource Alliance  
(<https://www.caddra.ca/wp-content/uploads/Canadian-ADHD-Practice-Guidelines-4.1-January-6-2021.pdf>)

Australia: Australasian ADHD Professionals Association  
(<https://aadpa.com.au/wp-content/uploads/2026/01/Australian-Clinical-Practice-Guideline-For-ADHD-Updated-January-2026.pdf>)

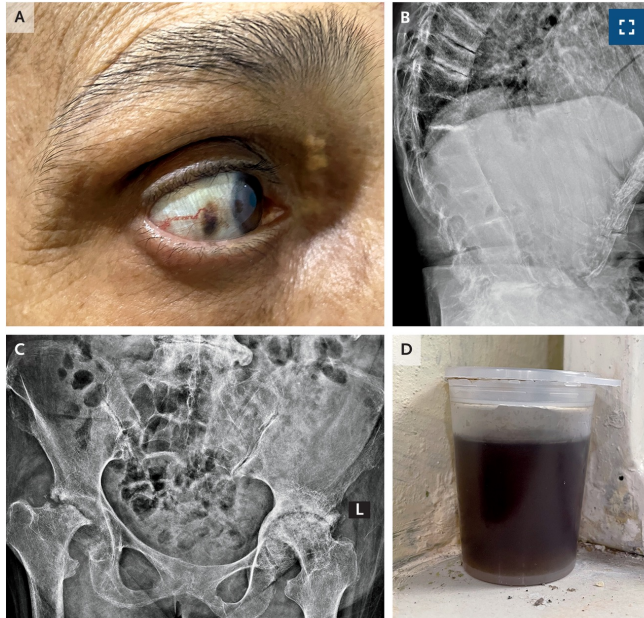
United States: guidelines forthcoming from American Professional Society of  
ADHD and Related Disorders  
(<https://www.apsard.org>)

## Conclusion and Recommendations

The case illustration describes a woman who first draws attention for burnout and performance-related anxiety, but on closer inspection also has symptoms of ADHD. Yet, this patient has never been diagnosed with ADHD or treated for this condition — a common occurrence. To best assess and treat this patient, it is essential to recognize the possibility that ADHD could be present; interview her and systematically assess the frequency, severity, and effect of ADHD symptoms with the use of a DSM-based rating scale; gather collateral information from her partner or parent; and assess for the presence of psychiatric and physical coexisting conditions. We would diagnose this patient with ADHD and coexisting generalized anxiety disorder and would prioritize ADHD treatment, because the ADHD symptoms precede and underlie the anxiety. We would educate the patient and her partner about ADHD and prescribe long-acting psychostimulant medication or a nonstimulant medication (which might also address the coexisting anxiety). We would expect treatment of ADHD symptoms to improve the ability to meet deadlines and enable the patient to better organize work and family life and thereby decrease anxiety. We would follow up frequently — every 2 to 4 weeks until the patient's condition is stable. If there are residual ADHD impairments after the medication dose is optimized, we would consider changing to or augmenting with a different medication or adding organizational-skills training. After the ADHD symptoms abate, we would reassess the level of anxiety. Psychosocial treatment for anxiety disorders is quite effective and would probably be the first choice if treatment for anxiety is to be added; however, a variety of medications, including selective serotonin-reuptake inhibitors, could also be used together with ADHD treatments.

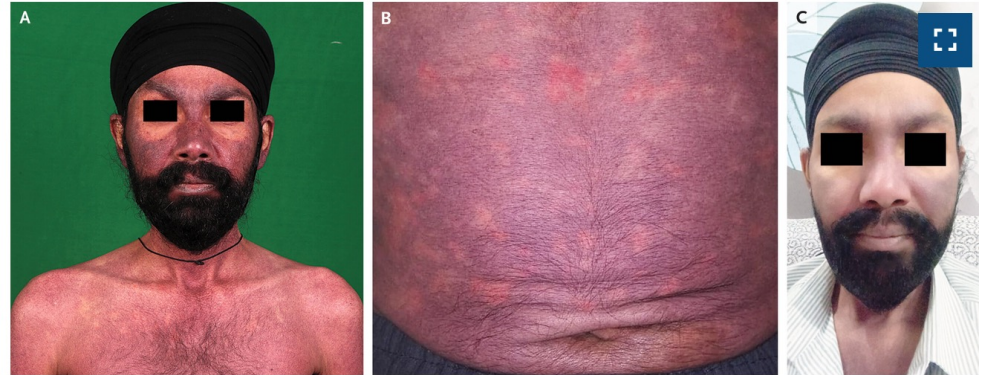


# Alkaptonuria



A 64-year-old woman with no known medical history presented to the rheumatology outpatient clinic with a 4-year history of worsening low back pain and difficulty walking. On examination, she had patches of darkly pigmented sclera (Panel A), kyphosis, and a Trendelenburg gait. Radiographs of the lumbosacral spine showed narrowing of the intervertebral disk space, disk-space calcification, and vertebral end-plate sclerosis (Panel B, lateral view). Radiographs of the pelvis showed destruction of the femoral heads (Panel C, anterior view). On further history taking, she reported that since childhood her urine had darkened when left sitting out. A urine sample turned black after being left out overnight at room temperature (Panel D). Urine levels of homogentisic acid were elevated. Molecular genetic testing was not available. A diagnosis of alkaptonuria was made. Alkaptonuria is an autosomal recessive disorder of tyrosine metabolism that results in high levels of homogentisic acid that subsequently polymerizes to form a pigment. The condition manifests in childhood with darkening of urine after oxidation by air and in adulthood with pigmentation of connective tissues (known as ochronosis) and early-onset, severe osteoarthropathy (known as ochronotic arthropathy). Treatment with nitisinone (an enzyme inhibitor that reduces homogentisic acid production) was initiated, and bilateral total hip replacement was performed. The patient was lost to follow-up 2 months after surgery.

# Flushing in Carcinoid Syndrome



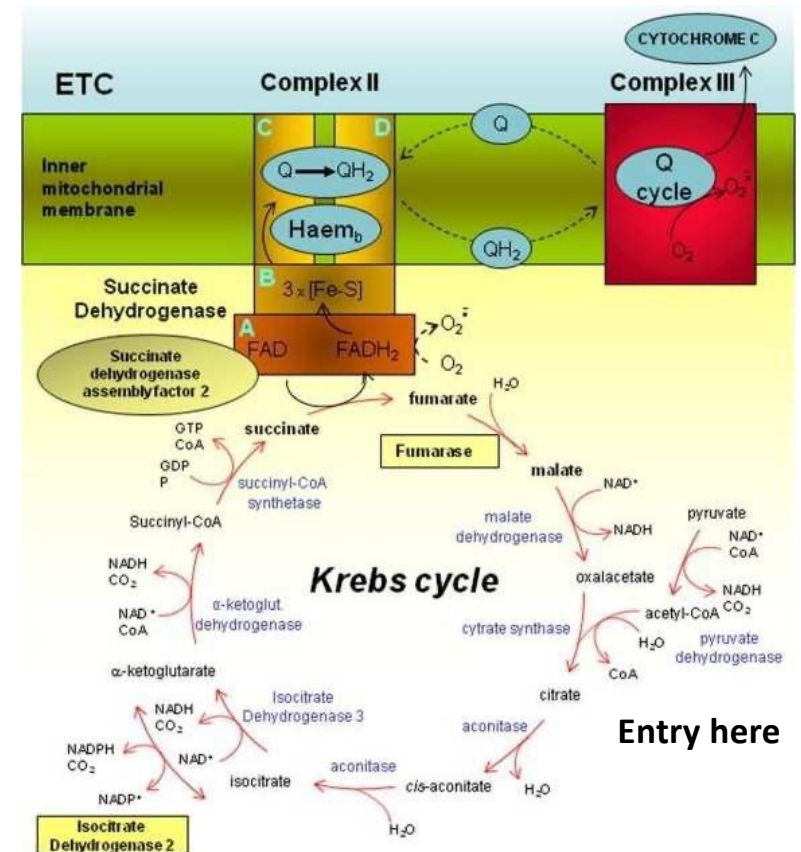
A 44-year-old man was admitted to a tertiary care hospital for the management of carcinoid syndrome. Four years earlier, he had received a diagnosis of carcinoid syndrome related to metastatic neuroendocrine cancer of unknown primary cause during an evaluation of episodic facial flushing, diarrhea, and dyspnea. Treatment with octreotide had been started, but the patient faced financial constraints that interfered with his ability to adhere to the therapy, and his symptoms had worsened. On physical examination at the current presentation, he had mottled, violaceous, blanchable flushing across the face (Panel A) and torso (Panel B). Flushing is the most common manifestation of carcinoid syndrome. It occurs when tumor cells (most commonly hepatic metastases) release vasoactive substances into the systemic circulation, which results in cutaneous vasodilation. Although flushing episodes typically manifest as transient discoloration of the face, neck, and upper chest, chronic episodes may lead to more-diffuse, persistent, and violaceous flushing, as well as to the development of telangiectasias. Laboratory studies showed high 24-hour urinary excretion of 5-hydroxyindoleacetic acid and high serum levels of chromogranin A. Positron-emission tomography-computed tomography with the use of gallium-68-dotatate identified numerous hepatic and skeletal metastases without a clear primary tumor. Intensified treatment of carcinoid syndrome was initiated. Four weeks later, the patient's flushing had abated considerably (Panel C [photograph taken by the patient]).



**Die Succinat-Dehydrogenase (SDH)** ist ein Protein-Komplex, der eine Doppelfunktion im Stoffwechsel erfüllt. Sie wirkt sowohl als Enzym im Citratzyklus (Zitronensäurezyklus) als auch als **Komplex II** der mitochondrialen Atmungskette (Elektronentransportkette).

### Hauptfunktionen

- **Katalyse:** Wandelt Succinat (Bernsteinsäure) in Fumarat um und oxidiert es dabei.
- **Elektronentransport:** Überträgt die gewonnenen Elektronen über ein kovalent gebundenes FAD (Flavin-Adenin-Dinukleotid) und Eisen-Schwefel-Cluster weiter auf Ubichinon (Coenzym Q), welches zu Ubichinol reduziert wird.
- **Besonderheit:** Im Gegensatz zu anderen Komplexen der Atmungskette pumpt die SDH **keine Protonen** ( $H^+$ ) durch die innere Mitochondrienmembran



**Mutations in succinate dehydrogenase (SDH) genes cause pheochromocytoma through a "pseudohypoxic" metabolic mechanism that tricks the cell into behaving as if it lacks oxygen.**

### **The Step-by-Step Mechanism**

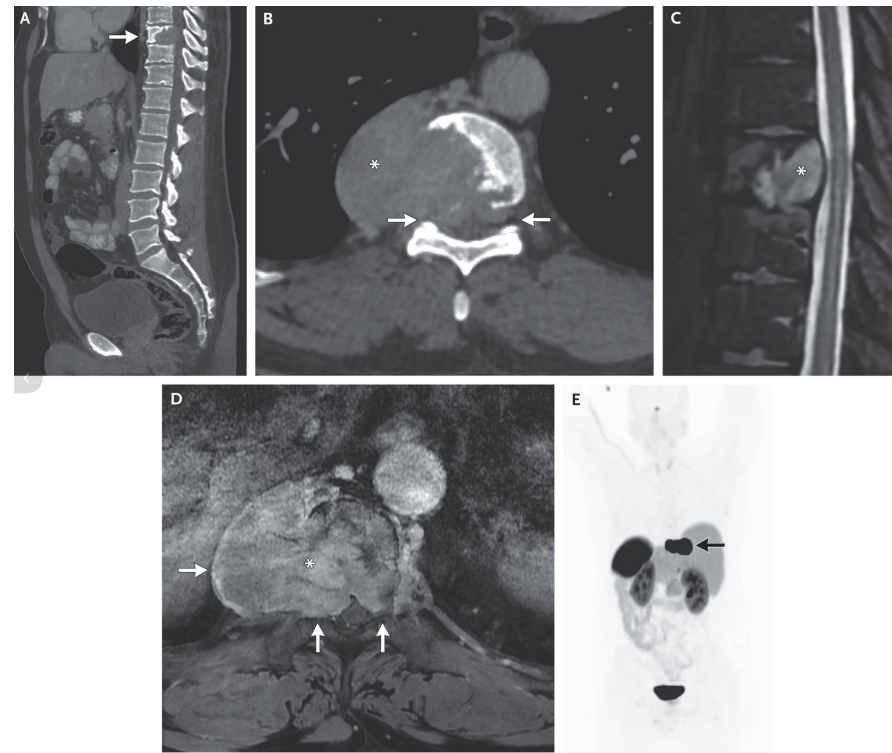
- **Loss of SDH Function:** Mutations in the genes encoding SDH subunits (*SDHA*, *SDHB*, *SDHC*, *SDHD*, or the assembly factor *SDHAF2*) impair mitochondrial complex II, which normally functions in both the Krebs cycle and the electron transport chain.
- **Succinate Accumulation:** Because the SDH enzyme cannot properly convert succinate to fumarate, high levels of succinate build up inside the mitochondria and spill into the cell's cytoplasm.
- **Inhibition of Prolyl Hydroxylases (PHDs):** The excess succinate blocks oxygen-sensing enzymes known as prolyl hydroxylases (specifically PHD2/EglN3).
- **Stabilization of HIF- $\alpha$ :** Normally, PHDs mark Hypoxia-Inducible Factor alpha (HIF- $\alpha$ ) for destruction when oxygen is present. When succinate inhibits PHDs, HIF- $\alpha$  escapes degradation and accumulates.
- **Tumorigenesis and Signaling:** High levels of HIF- $\alpha$  turn on genes that promote angiogenesis (blood vessel growth), cell survival, and metabolic shifting toward glycolysis. This unchecked cellular proliferation drives the development of neuroendocrine tumors in chromaffin cells, leading to pheochromocytomas and paragangliomas.



## Case 29-2026: A 39-Year-Old Man with Abdominal Pain, Foot Drop, and a Spinal Mass

A 39-year-old man was admitted to the neurosurgical service of this hospital because of abdominal pain and a spinal mass.

The patient had been in his usual state of health until 2 weeks before the current admission, when intermittent abdominal pain developed. He presented to a primary care clinic affiliated with this hospital. On evaluation, the patient reported a **17-year history of chronic midline lower-back pain** that had worsened recently. He noted that new pain was located in the mid-upper back and radiated around to the right upper quadrant. The pain was not related to meals or physical activity and did not awaken him from sleep. He had no nausea, fever, motor weakness, or bowel or bladder dysfunction. The physical examination showed no tenderness on palpation of the abdomen, and the **neurologic examination was normal**. Laboratory tests were ordered, and computed tomography (CT) of the abdomen and pelvis was scheduled.



PET-CT

On admission to the hospital, the patient provided additional history. He reported no weight loss, night sweats, headache, palpitations, flushing, diaphoresis, constipation, or bowel or bladder incontinence. The oral temperature was 36.2°C, the blood pressure 192/91 mm Hg, the pulse 78 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. No motor asymmetry, clonus, hyperreflexia, or other upper-motor-neuron signs were noted on examination of the lower legs. There was subtle neuropathic gait with a right foot drop, and sensation to light touch was symmetric. No hepatosplenomegaly or palpable lymphadenopathy was present, and there was no murmur on auscultation of the heart.

The medical history was notable for a traumatic brain injury that the patient had sustained while he was in the U.S. military, as well as chronic back pain, major depressive disorder, and attention deficit–hyperactivity disorder. Medications included bupropion and dextroamphetamine–amphetamine. The patient worked in construction and was an Iraq War veteran. During his time on active duty in Iraq, he had been exposed to burn pits. The family history was notable for spinal paraganglioma in his father, who had died at 38 years of age, and a recent diagnosis of multiple myeloma in his mother.

| Variable                             | Reference Range, Adults† | On Current Admission |
|--------------------------------------|--------------------------|----------------------|
| <b>Blood</b>                         |                          |                      |
| Hemoglobin (g/dl)                    | 13.5–17.5                | 16.5                 |
| Hematocrit (%)                       | 41.0–53.0                | 47.2                 |
| White-cell count (per $\mu$ l)       | 4000–11,000              | 5280                 |
| Differential count (per $\mu$ l)     |                          |                      |
| Neutrophils                          | 1920–7600                | 5350                 |
| Lymphocytes                          | 720–4100                 | 1360                 |
| Monocytes                            | 160–1100                 | 600                  |
| Eosinophils                          | 0–500                    | 150                  |
| Basophils                            | 0–150                    | 40                   |
| Immature granulocytes                | 0–90                     | 20                   |
| Platelet count (per $\mu$ l)         | 150,000–450,000          | 184,000              |
| Sodium (mmol/liter)                  | 135–145                  | 137                  |
| Potassium (mmol/liter)               | 3.4–5.0                  | 3.6                  |
| Chloride (mmol/liter)                | 98–108                   | 98                   |
| Carbon dioxide (mmol/liter)          | 23–32                    | 25                   |
| Urea nitrogen (mg/dl)                | 8–25                     | 11                   |
| Creatinine (mg/dl)                   | 0.60–1.30                | 0.97                 |
| Glucose (mg/dl)                      | 70–110                   | 86                   |
| Globulin (g/dl)                      | 1.9–4.1                  | 2.5                  |
| Albumin (g/dl)                       | 3.3–5.0                  | 4.9                  |
| Alanine aminotransferase (U/liter)   | 10–55                    | 13                   |
| Aspartate aminotransferase (U/liter) | 10–40                    | 16                   |
| Alkaline phosphatase (U/liter)       | 45–115                   | 132                  |
| Total bilirubin (mg/dl)              | 0.0–1.0                  | 0.6                  |
| Lactate dehydrogenase (U/liter)      | 110–210                  | 263                  |
| <b>Urine</b>                         |                          |                      |
| Color                                | Yellow                   | Yellow               |
| Clarity                              | Clear                    | Turbid               |
| pH                                   | 5.0–9.0                  | 5.5                  |
| Specific gravity                     | 1.001–1.035              | 1.010                |
| Glucose                              | Negative                 | Negative             |
| Ketones                              | Negative                 | Negative             |
| Leukocyte esterase                   | Negative                 | Negative             |
| Nitrite                              | Negative                 | Negative             |
| Blood                                | Negative                 | Negative             |
| Protein                              | Negative                 | Negative             |
| Erythrocytes (per high-power field)  | 0–2                      | 0–2                  |
| Leukocytes (per high-power field)    | <10                      | <10                  |
| Bacteria                             | None                     | None                 |

## Discussion

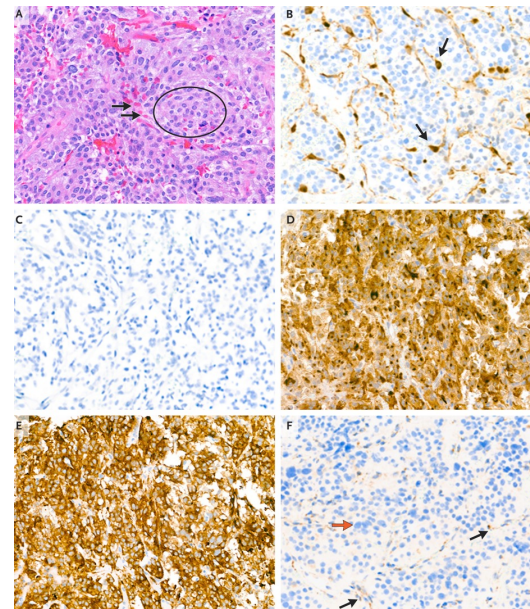
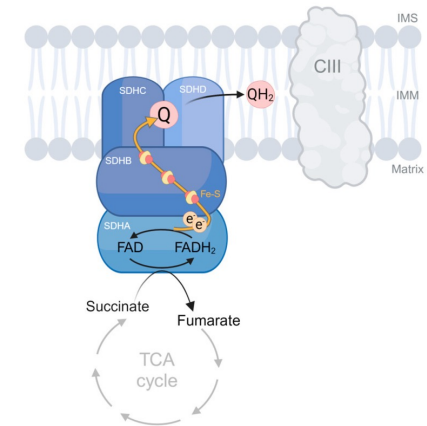
The history of paraganglioma in the patient's father made this tumor the leading diagnosis, given that 30 to 40% of paragangliomas are caused by germline variants in the genes encoding the succinate dehydrogenase (SDH) subunits (*SDHA*, *SDHB*, *SDHC*, and *SDHD*), or in *VHL*, *NF1*, or *RET*. These tumors are typically inherited in an autosomal dominant pattern. At this point, in addition to the pending results from percutaneous biopsy, a specimen of blood was obtained and a 24-hour urine collection was completed for measurement of norepinephrine, metanephrine, normetanephrine, dopamine, and 5-hydroxyindoleacetic acid levels. When the diagnosis of paraganglioma is suspected, I typically test for these hormones to see if the tumor is actively secreting catecholamines. In addition, nuclear imaging with positron-emission tomography (PET)–CT with gallium-68 (Ga-68)–dotatate was performed to quantify the extent of disease and reveal possible foci of metastasis. For a hormonally active tumor, adrenergic blockage should be initiated before surgical intervention to prevent a catecholamine storm that could lead to extreme hypertension and tachycardia in the perioperative period.



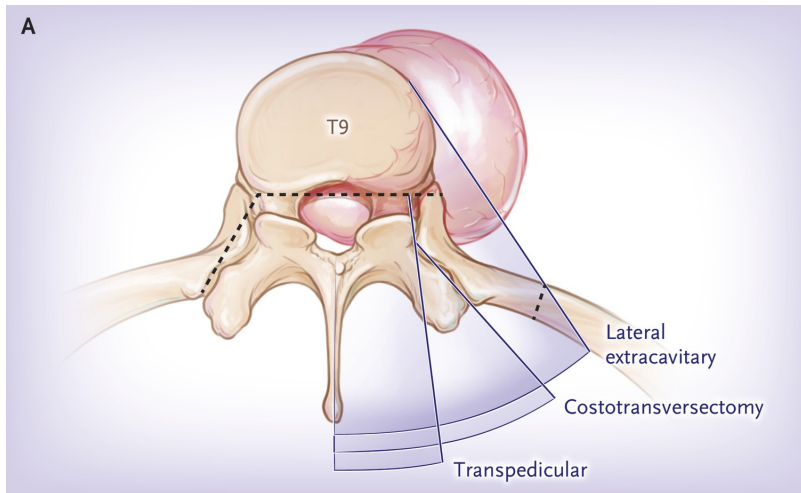
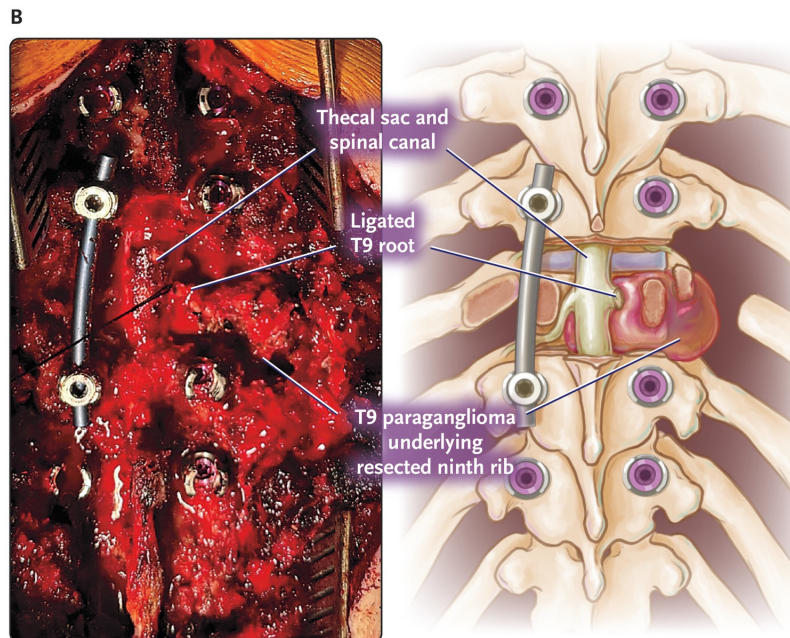
## Hospital Course

The patient had elevated serum levels of **chromogranin A (279 ng per milliliter;** reference value, <0.93), dopamine (43 pg per milliliter; reference value, <30), and normetanephrine (6.4 nmol per liter; reference value, <0.9). The serum level of metanephrine was normal (<0.2 nmol per liter; reference value, <0.5). The 24-hour urine collection revealed markedly elevated levels of norepinephrine (827  $\mu$ g; reference range, 15 to 80), metanephrine (6640  $\mu$ g; reference range, 200 to 614), and normetanephrine (6493  $\mu$ g; reference range, 111 to 419), as well as elevated levels of dopamine (449  $\mu$ g; reference range, 65 to 400) and 5-hydroxyindoleacetic acid (11.3  $\mu$ g; reference value, <8.2). A subsequent upper endoscopy showed no abnormalities, and a colonoscopy was notable for a large, serrated adenoma without malignant features.

PET-CT with Ga-68–dotatate showed intense radiotracer uptake by the spinal mass, without any other uptake elsewhere in the body.



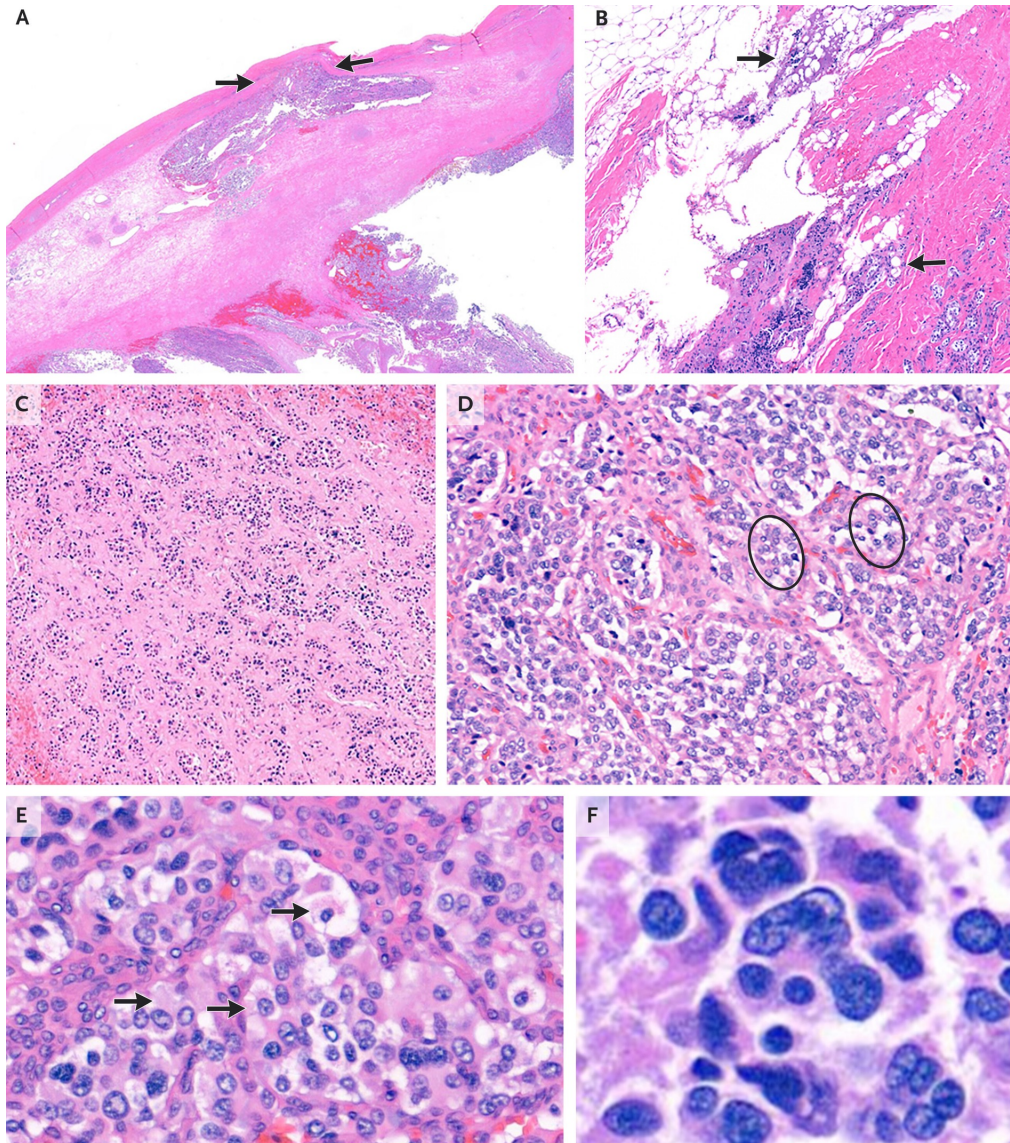
Immunohistochemical staining for S100 (Panel B) highlights the sustentacular cells around the nests of chief cells (arrows). Cytokeratin MNF11 staining (Panel C) is negative in tumor cells, whereas staining for chromogranin A and synaptophysin (Panels D and E, respectively) is positive in tumor cells. Succinate dehydrogenase B staining (Panel F) shows that granular cytoplasmic staining is absent in tumor cells (red arrow) but is preserved in endothelial cells (black arrows), which serve as an internal control.



## Surgical Approaches and an Intraoperative Photograph.

Panel A shows various approaches to the surgical procedure indicated in this patient. Posterolateral access to a mass compressing the ventral aspect of the thecal sac of the thoracic spine can be attained with the transpedicular approach, the costotransversectomy approach, or the lateral extracavitary approach. These approaches provide progressively increased visualization of abnormalities that cross the midline or paravertebral region.<sup>6</sup> Panel B shows a photograph obtained during the patient's surgical procedure. The thecal sac and paravertebral paraganglioma are visible along the T9 vertebral body after T8–T9 and T9–T10 laminectomy, resection of the T9 pedicles and ninth rib, and ligation of the right T9 nerve root.





### Excision Specimen.

Hematoxylin and eosin staining of the excised spinal mass shows a thick fibrous capsule surrounding the tumor, with focal areas of capsular invasion (Panel A, arrows). There is evidence of infiltration of the tumor into the surrounding fibroadipose tissue (Panel B, arrows), nests of tumor cells with degenerative changes and conspicuous fibrosis (Panel C), and a focal area with tumor cells forming more rounded nests (Panel D, ovals). Clear-cell changes in the cytoplasm and flocculent eosinophilic cytoplasmic inclusions are seen (Panel E, arrows). Increased cellular pleomorphism is characterized by enlarged nuclei and irregular nuclear membrane contours (Panel F).

**Pathological Diagnosis**  
**Extraadrenal paraganglioma.**

# THE LANCET

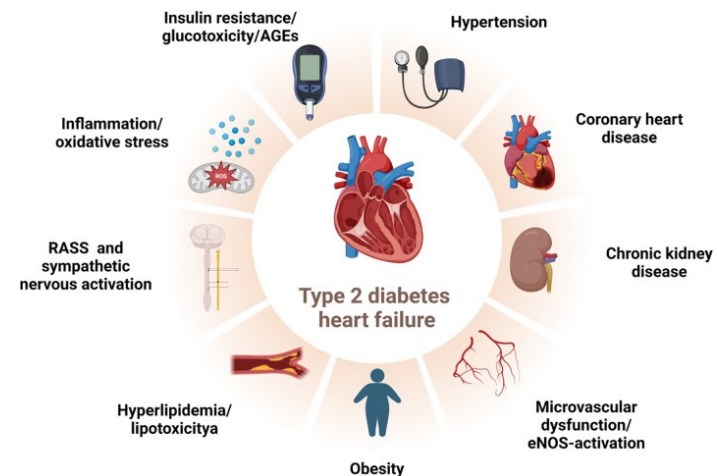
**MACE** steht für *Major Adverse Cardiovascular Events* (schwerwiegende unerwünschte kardiovaskuläre Ereignisse). Bei Menschen mit Typ-2-Diabetes bezeichnet dieser Begriff eine standardisierte Kombination aus:

- **kardiovaskulärem Tod**
- **nicht-tödlichem Myokardinfarkt** (Herzinfarkt)
- **nicht-tödlichem Schlaganfall**

## Zusammenhang zwischen Typ-2-Diabetes und MACE

- **Erhöhtes Risiko:** Typ-2-Diabetes schädigt langfristig die Blutgefäße (Atherosklerose) und verdoppelt bzw. erhöht das Risiko für schwere Herz-Kreislauf-Ereignisse signifikant – unabhängig von anderen Vorerkrankungen.
- **Haupttodesursache:** Kardiovaskuläre Komplikationen sind die häufigste Ursache für schwere Krankheitsverläufe und Sterblichkeit bei Typ-2-Diabetes.

**No, insulin does not reduce the risk of Major Adverse Cardiovascular Events (MACE) in type 2 diabetes.**



# Cardiovascular safety of orforglipron versus insulin glargine in adults with type 2 diabetes at increased cardiovascular risk (ACHIEVE-4): a phase 3, event-driven, randomised, open-label, non-inferiority, active comparator trial

## Summary

**Background** Orforglipron is an oral, non-peptide GLP-1 receptor agonist. While some peptide GLP-1 receptor agonists have established cardiovascular benefit, the cardiovascular safety of non-peptide GLP-1 receptor agonists has not been studied. This study aimed to compare the effect of orforglipron with insulin glargine on the incidence of major adverse cardiovascular events in individuals with type 2 diabetes and obesity or overweight who are at increased risk for cardiovascular events.

**Methods** This event-driven, phase 3, multicentre, randomised, open-label, active comparator, parallel-group study was conducted in 317 sites across 16 countries and territories. Adults with type 2 diabetes at increased cardiovascular risk with glycated haemoglobin (HbA<sub>1c</sub>) concentrations between 7·0% and 10·5% (53–91 mmol/mol) and a BMI of 25 kg/m<sup>2</sup> or more, treated with up to three glucose-lowering medications (metformin, a sulfonylurea, and/or an SGLT2 inhibitor), were randomly assigned (1:1) to oral orforglipron maximum tolerated dose (up to 36 mg capsule [equivalent to 17·2 mg tablet]) or injectable titrated insulin glargine, each administered once daily. All participants had established cardiovascular or chronic kidney disease. The primary outcome was time to occurrence of four-component major adverse cardiovascular events (MACE-4), including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina. Non-inferiority of orforglipron to insulin glargine was declared if the upper limit of the two-sided 95% CI for the hazard ratio (HR; orforglipron vs insulin glargine) was less than 1·8. The primary endpoint and other safety endpoints were assessed in all participants who took at least one dose of assigned treatment using all datapoints from baseline until withdrawal or study completion, regardless of treatment adherence. This trial was registered on ClinicalTrials.gov (NCT05803421) and is completed.



**Findings** Between May 1, 2023, and Sept 5, 2024, 2749 participants were randomly assigned (1371 to orforglipron and 1378 to insulin glargine). 1032 (37·5%) participants were female and 1717 (62·5%) male. 2362 (85·9%) participants had established cardiovascular disease and 1033 (37·6%) had chronic kidney disease. Mean baseline age, HbA<sub>1c</sub>, and BMI were 63·1 years (SD 9·9), 8·2% (1·0), and 33 kg/m<sup>2</sup> (6·2), respectively. Over a median follow-up of 2 years, the primary outcome occurred in 57 (4·2%) of 1358 orforglipron participants and 67 (5·0%) of 1343 insulin glargine participants, showing non-inferiority to insulin glargine for MACE-4 (HR 0·84; 95% CI 0·59–1·20;  $p < 0·0001$  for non-inferiority). Gastrointestinal adverse events were reported in 851 (62·1%) of 1371 orforglipron participants and 193 (14·2%) of 1355 insulin glargine participants; clinically significant or severe hypoglycaemia (glucose  $< 3$  mmol/L [54 mg/dL]) occurred in 93 (6·8%) of 1371 orforglipron participants and 260 (19·2%) of 1355 insulin glargine participants. 62 deaths were reported during the study: 19 (1·4%) of 1371 participants receiving orforglipron and 43 (3·2%) of 1355 participants receiving insulin glargine; all deaths except one (in the insulin glargine group) were deemed unrelated to treatment.

**Interpretation** In people with type 2 diabetes at increased cardiovascular risk, the cardiovascular safety of orforglipron was confirmed by demonstrating non-inferiority to insulin glargine for MACE-4. Gastrointestinal adverse events were the most frequent adverse event and most common reason for orforglipron treatment discontinuation with orforglipron, while clinically significant hypoglycaemia occurred less frequently with orforglipron than with insulin glargine. These findings support orforglipron as a potential once-daily, oral treatment option with established cardiovascular safety in people with type 2 diabetes and increased cardiovascular risk.

**Funding** Eli Lilly and Company.



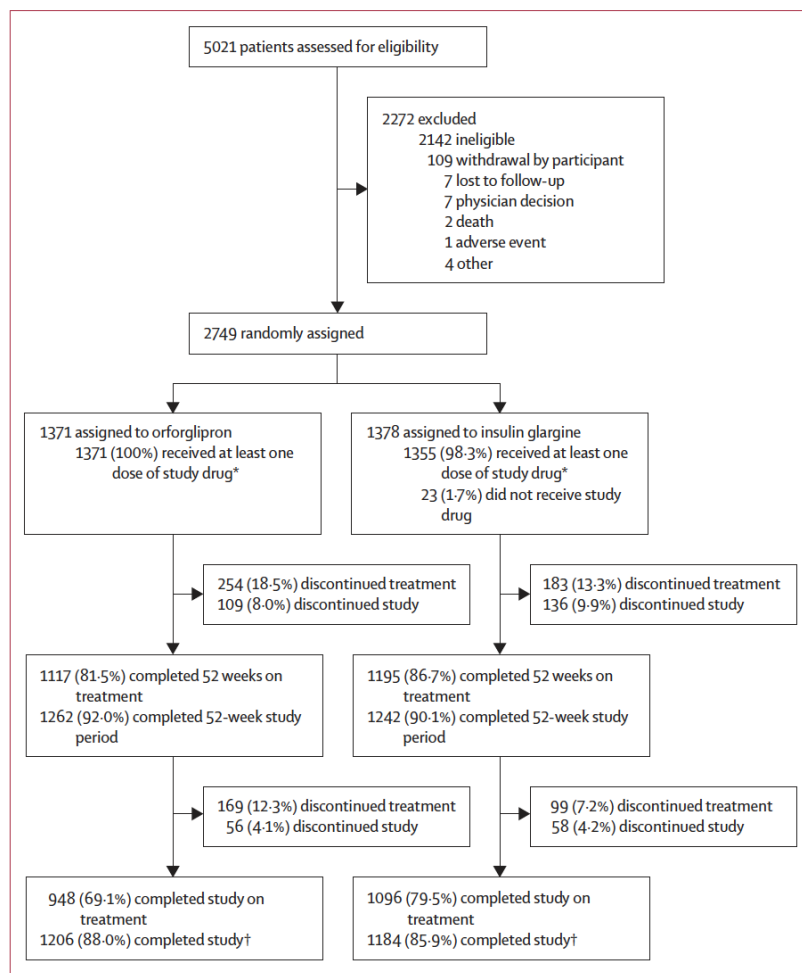


**Figure 1: Trial profile**

Note: 25 participants (12 insulin glargine, 13 orforglipron) from sites closed during the trial due to GCP non-compliance were excluded from analyses of primary and key secondary endpoints. Orforglipron refers to either 36 mg (equivalent to 17.2 mg tablet) or maximum tolerated dose. GCP=good clinical practice. \* Safety population. †Median follow-up duration 103.9 weeks (IQR 84.0–116.6).

|                                                 | Orforglipron<br>(n=1371) | Insulin glargine<br>(n=1378) | Total<br>(N=2749) |
|-------------------------------------------------|--------------------------|------------------------------|-------------------|
| Age, years                                      | 63.2 (10.0)              | 63.1 (9.8)                   | 63.1 (9.9)        |
| Sex                                             |                          |                              |                   |
| Female                                          | 511 (37.3%)              | 521 (37.8%)                  | 1032 (37.5%)      |
| Male                                            | 860 (62.7%)              | 857 (62.2%)                  | 1717 (62.5%)      |
| Race                                            |                          |                              |                   |
| American Indian or Alaska Native                | 148/1366 (10.8%)         | 137/1372 (10.0%)             | 285/2738 (10.4%)  |
| Asian                                           | 114/1366 (8.3%)          | 118/1372 (8.6%)              | 232/2738 (8.5%)   |
| Black or African American                       | 120/1366 (8.8%)          | 107/1372 (7.8%)              | 227/2738 (8.3%)   |
| Native Hawaiian or Other Pacific Islander       | 2/1366 (0.1%)            | 1/1372 (0.1%)                | 3/2738 (0.1%)     |
| White                                           | 944/1366 (69.1%)         | 970/1372 (70.7%)             | 1914/2738 (69.9%) |
| Ethnicity                                       |                          |                              |                   |
| Hispanic or Latino                              | 631 (46.0%)              | 645/1377 (46.8%)             | 1276/2748 (46.4%) |
| Not Hispanic or Latino                          | 740 (54.0%)              | 732/1377 (53.2%)             | 1472/2748 (53.6%) |
| Duration of type 2 diabetes, years              | 11.9 (8.3)               | 12.1 (8.5)                   | 12.0 (8.4)        |
| HbA <sub>1c</sub> concentration                 |                          |                              |                   |
| In %                                            | 8.23 (1.0)               | 8.23 (1.0)                   | 8.23 (1.0)        |
| In mmol/mol                                     | 66.4 (11.0)              | 66.4 (10.7)                  | 66.4 (10.9)       |
| Fasting serum glucose                           |                          |                              |                   |
| In mg/dL                                        | 154.9 (47.3)             | 154.8 (48.0)                 | 154.9 (47.7)      |
| In mmol/L                                       | 8.6 (2.6)                | 8.6 (2.7)                    | 8.6 (2.7)         |
| Weight, kg                                      | 90.8 (20.0)              | 91.0 (20.1)                  | 90.9 (20.0)       |
| BMI, kg/m <sup>2</sup>                          | 32.6 (6.3)               | 32.6 (6.1)                   | 32.6 (6.2)        |
| Waist circumference, cm                         | 109.2 (14.1)             | 109.1 (14.2)                 | 109.2 (14.2)      |
| hsCRP, mg/L*                                    | 2.21 (189.2)             | 2.26 (177.8)                 | 2.24 (183.4)      |
| Systolic blood pressure, mm Hg                  | 130.1 (14.4)             | 131.6 (14.9)                 | 130.9 (14.7)      |
| Diastolic blood pressure, mm Hg                 | 77.3 (9.2)               | 77.9 (9.2)                   | 77.6 (9.2)        |
| Pulse rate, beats per minute                    | 71.8 (10.5)              | 72.4 (10.6)                  | 72.1 (10.6)       |
| Lipid parameters, mg/dL                         |                          |                              |                   |
| Total cholesterol                               | 156.2 (48.5)             | 159.2 (50.8)                 | 157.7 (49.7)      |
| Non-HDL cholesterol                             | 113.4 (44.1)             | 116.0 (45.4)                 | 114.7 (44.7)      |
| HDL cholesterol                                 | 42.2 (11.0)              | 42.6 (11.3)                  | 42.4 (11.1)       |
| LDL cholesterol                                 | 79.3 (37.1)              | 80.9 (37.9)                  | 80.1 (37.5)       |
| VLDL cholesterol                                | 32.1 (14.2)              | 32.4 (14.3)                  | 32.2 (14.2)       |
| Triglycerides                                   | 174.8 (110.5)            | 181.4 (133.1)                | 178.1 (122.4)     |
| Free fatty acids, mmol/L                        | 0.60 (0.25)              | 0.60 (0.24)                  | 0.60 (0.25)       |
| History of cardiovascular disease               | 1178 (85.9%)             | 1184 (85.9%)                 | 2362 (85.9%)      |
| Coronary heart disease                          | 695 (50.7%)              | 668 (48.5%)                  | 1363 (49.6%)      |
| Congestive heart failure†                       | 276 (20.1%)              | 276 (20.0%)                  | 552 (20.1%)       |
| Peripheral arterial disease                     | 250 (18.2%)              | 251 (18.2%)                  | 501 (18.2%)       |
| Cerebrovascular disease                         | 197 (14.4%)              | 232 (16.8%)                  | 429 (15.6%)       |
| eGFR-cystatin-C†, mL/min per 1.73m <sup>2</sup> | 69.1 (24.2)              | 69.1 (23.6)                  | 69.1 (23.9)       |
| <60 mL/min per 1.73m <sup>2</sup>               | 527 (38.5%)              | 506 (36.7%)                  | 1033 (37.6%)      |
| UACR, mg/g                                      | 14.0 (7.0–39.0)          | 15.0 (7.0–46.0)              | 14.0 (7.0–41.5)   |
| Macroalbuminuria (UACR >300 mg/g)               | 82/1263 (6.5%)           | 93/1258 (7.4%)               | 175/2521 (6.9%)   |
| Microalbuminuria (UACR 30–300 mg/g)             | 300/1263 (23.8%)         | 308/1258 (24.5%)             | 608/2521 (24.1%)  |
| Diabetic retinopathy‡                           | 272/1371 (19.8%)         | 295/1355 (21.8%)             | 567/2726 (20.8%)  |

Data are n (%), n/N (%), mean (SD), or median (IQR) and from all randomised participants unless stated otherwise. For race, ethnicity, macroalbuminuria, and microalbuminuria, the denominators are the number of participants with non-missing data. Orforglipron refers to either 36 mg (equivalent to 17.2 mg tablet) or maximum tolerated dose. eGFR=estimated glomerular filtration rate. HbA<sub>1c</sub>=glycated haemoglobin. hsCRP=high-sensitivity C-reactive protein. UACR=urinary albumin-to-creatinine ratio. \*Values are mean (coefficient of variation). †Includes New York Heart Association Class II and III. ‡eGFR was calculated by CKD-EPI cystatin-C equation. §Percentages are based on safety population, assessed from fundus photography evaluations.

**Table 1: Baseline demographics and clinical characteristics**

|                                     | Orforglipron   | Insulin glargine | HR (95% CI)      | p value                   |
|-------------------------------------|----------------|------------------|------------------|---------------------------|
| MACE-4 (primary endpoint)*          | 57/1358 (4.2%) | 67/1343 (5.0%)   | 0.84 (0.59–1.20) | <0.0001 (non-inferiority) |
| Cardiovascular death                | 14/1358 (1.0%) | 29/1343 (2.2%)   | 0.47 (0.25–0.90) | ..                        |
| Non-fatal myocardial infarction     | 19/1358 (1.4%) | 22/1343 (1.6%)   | 0.85 (0.46–1.58) | ..                        |
| Non-fatal stroke                    | 14/1358 (1.0%) | 14/1343 (1.0%)   | 0.98 (0.47–2.06) | ..                        |
| Hospitalisation for unstable angina | 14/1358 (1.0%) | 9/1343 (0.7%)    | 1.55 (0.67–3.58) | ..                        |
| MACE-3 (key secondary endpoint)*    | 46/1358 (3.4%) | 59/1366 (4.3%)   | 0.77 (0.52–1.13) | 0.18                      |

Data are n/N (%) unless otherwise stated; the numerator refers to the number of participants with an event, and the denominator refers to the number of participants in the specific analysis population. Orforglipron refers to either 36 mg (equivalent to 17.2 mg tablet) or maximum tolerated dose. All events were confirmed by the clinical endpoint committee. Deaths adjudicated to undetermined cause were included as cardiovascular deaths. Point estimate and 95% CI of HR comparing orforglipron and insulin glargine were obtained from time-to-first-event analysis using Cox proportional hazards model. Non-inferiority analysis of MACE-4 was performed in the safety analysis set (randomised participants excluding those that did not receive at least one dose of study drug [23 participants in the insulin group] and those from sites closed due to GCP non-compliance [12 insulin glargine, 13 orforglipron]). MACE-3 analysis for superiority was performed in all randomised participants excluding participants from sites closed due to GCP non-compliance (12 insulin glargine, 13 orforglipron). p values are for superiority testing, unless otherwise specified. GCP=good clinical practice. HR=hazard ratio. MACE-3=three-component major adverse cardiovascular events. MACE-4=four-component major adverse cardiovascular events. \* Controlled for family-wise type I error.

**Table 2: Summary of primary and key secondary cardiovascular outcomes**

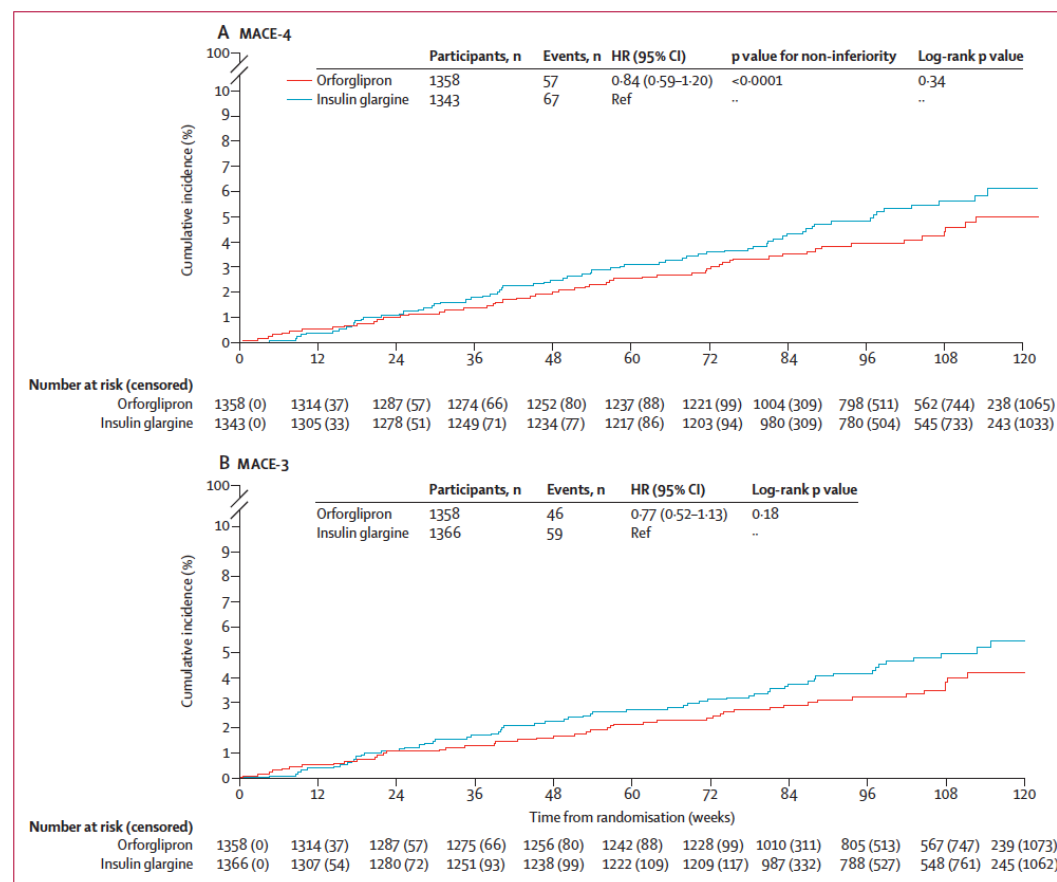


**Figure 2: Time to first occurrence of primary and key secondary cardiovascular outcomes**

All events confirmed by the clinical endpoint committee. Point estimate and 95% CI of HR comparing orforglipron and insulin glargine were obtained from time-to-first-event analysis using Cox proportional hazards model. Non-inferiority analysis of MACE-4 was performed in the safety analysis set (randomised participants excluding those that did not receive at least one dose of study drug [23 participants in the insulin group] and those from sites closed due to GCP non-compliance [12 insulin glargine, 13 orforglipron]). MACE-3 analysis for superiority was performed in all randomised participants excluding participants from sites closed due to GCP non-compliance (12 insulin glargine, 13 orforglipron). p values are for superiority testing, unless otherwise specified. Orforglipron refers to either 36 mg (equivalent to 17.2 mg tablet) or maximum tolerated dose. GCP=good clinical practice. HR=hazard ratio. MACE-3=three-component major adverse cardiovascular events (composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death). MACE-4=four-component major adverse cardiovascular events (composite of non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina, or cardiovascular death).

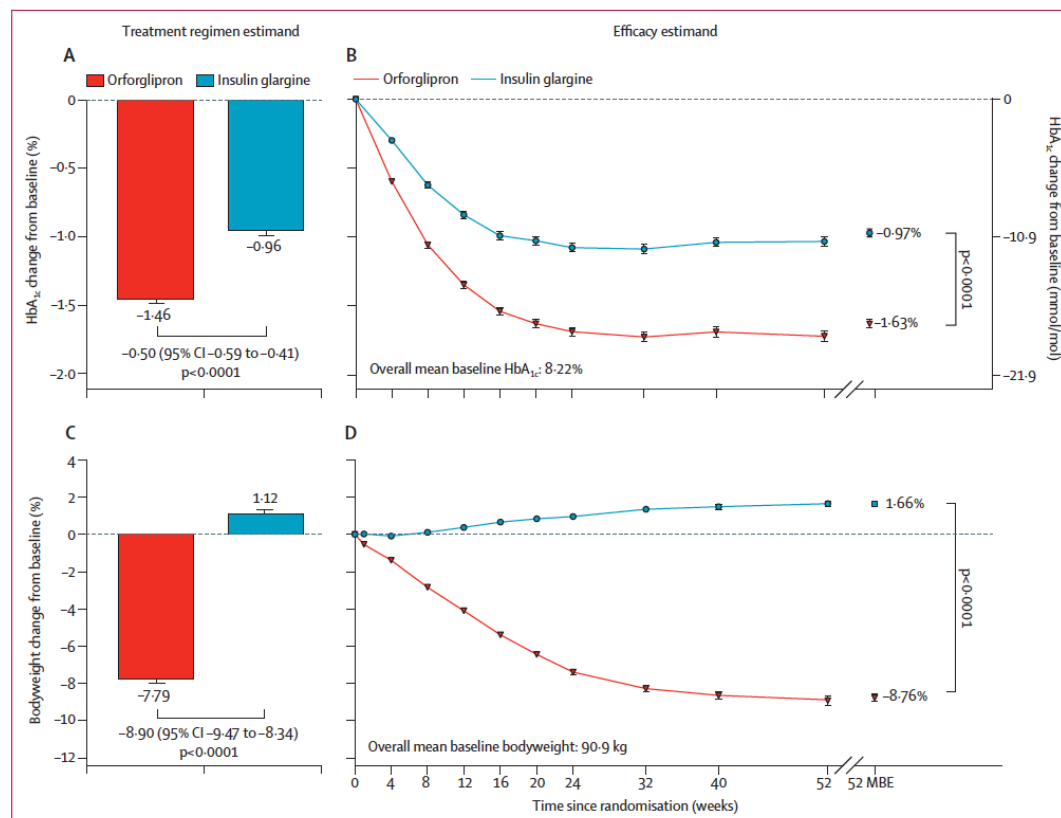


**Figure 3: Change from baseline in HbA<sub>1c</sub> and bodyweight at week 52**

Data in line plot are observed mean (SE). In A and C, treatment regimen estimand analysis was conducted using ANCOVA on randomised participants and treatment regimen estimand datapoints set, with missing data imputed. In B and D, efficacy estimand analysis was conducted using a mixed model for repeated measures on randomised participants and efficacy estimand datapoints set. Family-wise type I error was controlled for week 52. p values are for MBE change difference versus insulin glargine. Orforglipron refers to either 36 mg (equivalent to 17.2 mg tablet) or maximum tolerated dose. HbA<sub>1c</sub>=glycated haemoglobin. MBE=model-based estimate.

|                                                                            | Orforglipron<br>(n=1371) | Insulin glargine<br>(n=1355) |
|----------------------------------------------------------------------------|--------------------------|------------------------------|
| Participants with ≥1 TEAE                                                  | 1129 (82.3%)             | 922 (68.0%)                  |
| Adverse events leading to study treatment discontinuation                  | 211 (15.4%)              | 73 (5.4%)                    |
| Serious adverse events                                                     | 222 (16.2%)              | 255 (18.8%)                  |
| Death*                                                                     | 19 (1.4%)                | 43 (3.2%)                    |
| Gastrointestinal adverse events leading to study treatment discontinuation | 122 (8.9%)               | 3 (0.2%)                     |
| TEAEs in ≥5% of participants                                               |                          |                              |
| Nausea                                                                     | 438 (31.9%)              | 19 (1.4%)                    |
| Vomiting                                                                   | 288 (21.0%)              | 22 (1.6%)                    |
| Diarrhoea                                                                  | 280 (20.4%)              | 66 (4.9%)                    |
| Decreased appetite                                                         | 175 (12.8%)              | 5 (0.4%)                     |
| Constipation                                                               | 174 (12.7%)              | 19 (1.4%)                    |
| Dyspepsia                                                                  | 146 (10.6%)              | 13 (1.0%)                    |
| Abdominal distension                                                       | 93 (6.8%)                | 6 (0.4%)                     |
| Diabetic retinopathy                                                       | 79 (5.8%)                | 86 (6.3%)                    |
| Hypertension                                                               | 59 (4.3%)                | 73 (5.4%)                    |
| Other adverse events of interest                                           |                          |                              |
| Hypoglycaemia <54 mg/dL (level 2) or severe hypoglycaemia (level 3)†       | 93 (6.8%)                | 260 (19.2%)                  |
| Participants on sulfonylurea at baseline                                   | 63/494 (12.8%)           | 127/495 (25.7%)              |
| Participants not on sulfonylurea at baseline                               | 30/877 (3.4%)            | 133/860 (15.5%)              |
| Severe hypoglycaemia (level 3)†                                            | 1 (0.1%)                 | 12 (0.9%)                    |
| Adjudication-confirmed pancreatitis                                        | 2 (0.1%)                 | 3 (0.2%)                     |
| Gallbladder and biliary disorders                                          | 21 (1.5%)                | 22 (1.6%)                    |
| Cholelithiasis                                                             | 12 (0.9%)                | 11 (0.8%)                    |

Data are n (%) or n/N (%). For the section on hypoglycaemia stratified by baseline sulfonylurea use, the denominators are the number of participants receiving or not receiving a sulfonylurea at baseline. Orforglipron refers to either 36 mg (equivalent to 17.2 mg tablet) or maximum tolerated dose. Safety analyses were conducted in the safety analysis set (all participants who received ≥1 dose of study treatment). TEAEs and serious adverse events were those occurring from first dose through the end of the on-treatment period (including follow-up). Hypoglycaemia was classified according to the American Diabetes Association definitions: level 2, blood glucose <54 mg/dL (3.0 mmol/L); level 3, severe event characterised by altered mental and/or physical status requiring assistance. TEAE=treatment-emergent adverse event. \*Death is also included as a serious adverse event and in discontinuations due to adverse events. †Severe hypoglycaemia is characterised by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia; numbers for hypoglycaemia exclude hypoglycaemic events occurring after initiation of any new antihyperglycaemic therapy.

**Table 3: Safety and adverse events**

## Research in context

### Evidence before this study

We searched PubMed from database inception to Sept 2, 2026, with no language restriction, using the terms “GLP-1 receptor agonist” or “GLP-1 RA” or “orforglipron” and “type 2 diabetes”, and limited to clinical trials. GLP-1 receptor agonists are an established treatment for type 2 diabetes, with demonstrated benefits on glycaemic levels, bodyweight, and, for several injectable agents and oral semaglutide, cardiovascular outcomes. Orforglipron is a non-peptide, small-molecule GLP-1 receptor agonist developed for once-daily oral administration without food or fluid intake timing restrictions. In earlier phase 3 trials in the ACHIEVE programme, orforglipron showed clinically meaningful reductions in glycated haemoglobin (HbA<sub>1c</sub>) and bodyweight compared with placebo, dapagliflozin, or oral semaglutide, with a safety profile generally consistent with other GLP-1 receptor agonists. Additionally, improvements in cardiometabolic risk markers with orforglipron were observed both in the ACHIEVE and ATTAIN clinical programmes. To date, no clinical studies have assessed the cardiovascular safety of orforglipron nor any other small-molecule GLP-1 receptor agonist in participants with type 2 diabetes at increased cardiovascular risk.

### Added value of this study

This study was the first to assess the long-term cardiovascular safety of orforglipron compared with titrated basal insulin in more than 2700 participants with type 2 diabetes and overweight or obesity, at increased cardiovascular risk, followed up for a median of 104 weeks. By demonstrating non-inferiority of orforglipron to insulin glargine for four-component major adverse cardiovascular events (MACE-4; cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina), the study provides evidence for the cardiovascular safety of orforglipron

as required by contemporary regulatory guidance. The study also provides the first evidence that improvements in glycaemic control and bodyweight with orforglipron can be maintained over 104 weeks. Previously observed effects of orforglipron on additional cardiometabolic risk factors were confirmed in individuals at increased cardiovascular risk, and new findings in this study suggest orforglipron might be associated with improvements in markers of kidney function and damage. As the longest study of orforglipron completed to date, our findings also provide long-term (up to 104 weeks) safety data for orforglipron in participants already treated with a combination of one to three glucose-lowering medications commonly used in clinical practice, confirming no new safety signals beyond the known safety profile of orforglipron in shorter-term studies and that of other GLP-1 receptor agonists.

### Implications of all the available evidence

The ACHIEVE-4 trial completes the phase 3 development of orforglipron, the first oral small molecule that activates the GLP-1 pathway. In the ACHIEVE programme, once-daily oral orforglipron provided improvements in glycaemic control and bodyweight across the continuum of type 2 diabetes, including in participants with varying disease duration, diverse comorbidities, and a broad range of background glucose-lowering medications, with a safety profile generally consistent with that of other GLP-1 receptor agonists. The results of ACHIEVE-4 support the cardiovascular safety of once-daily oral orforglipron, demonstrating no excess cardiovascular risk with orforglipron compared with insulin glargine in people with type 2 diabetes and increased cardiovascular risk. Therefore, orally administered small molecules have the potential to retain the pharmacological benefits of peptide-based GLP-1 receptor agonists while providing a convenient route of administration to meet the needs and preferences of people living with type 2 diabetes.

**Gelbfieber** ist eine durch das Gelbfiebervirus (ein Flavivirus) verursachte, akute und potentiell lebensbedrohliche Infektionskrankheit, die durch den Stich infizierter Stechmücken (insbesondere *Aedes aegypti*) übertragen wird.

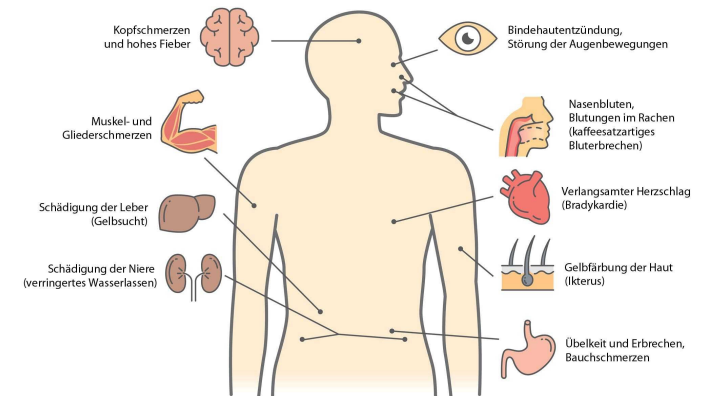
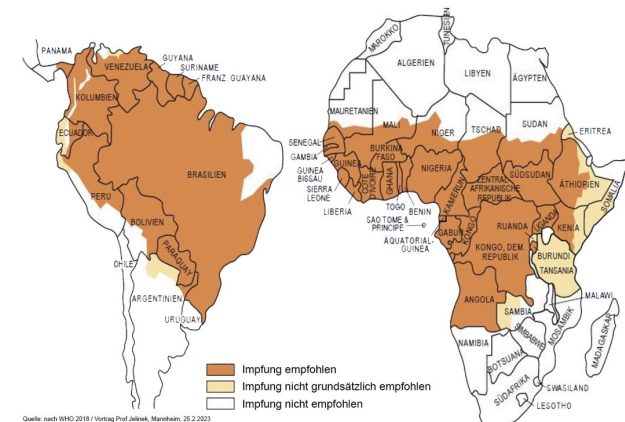
## Vorkommen und Verbreitung

- **Regionen:** Tropische und subtropische Gebiete in Subsahara-Afrika und Süd-/Mittelamerika.
- **Freie Zonen:** Asien, die Karibik und Europa sind gelbfieberfrei.

## Symptome und Krankheitsverlauf

- **Inkubationszeit:** 3 bis 6 Tage nach dem Mückenstich.
- **Phase 1 (milder/akuter Verlauf):** Plötzliches hohes Fieber, Schüttelfrost, Kopf-, Rücken- und Gliederschmerzen, Übelkeit und Erbrechen. Viele Betroffene erholen sich nach einigen Tagen.
- **Phase 2 (schwere/toxische Phase):** Nach einer kurzen Besserung von ein bis zwei Tagen kommt es bei ca. 10–20 % der Erkrankten zu schweren Organmanifestationen (Gelbsucht/Ikterus durch Leberschäden, Nierenversagen, Blutungen und Schockzustand). Die Sterblichkeit in dieser Phase liegt bei bis zu 50 %.

## Symptome des Gelbfiebers





# Immunogenicity of fractional one-fifth and one-half doses of 17DD yellow fever vaccine compared with full dose in children aged 9–23 months in Uganda: a phase 4, single-blind, randomised clinical trial

## Summary

**Background** Fractional doses of yellow fever vaccines have been shown to be safe and immunogenic in randomised controlled trials in adults and children. However, little evidence still remains in children younger than 2 years. We assessed immunogenicity of one-fifth (0·1 mL) and one-half (0·25 mL) fractional doses compared with full doses of 17DD yellow fever vaccine in children aged 9–23 months in Kampala, Uganda.

**Methods** This phase 4, single-blind, randomised clinical trial evaluating fractional dose 17DD yellow fever vaccine among children was conducted at three public-sector health facilities in Uganda. Eligible participants were aged 9–23 months at enrolment, had no history of yellow fever disease or vaccination, and did not meet the exclusion criteria. Children were enrolled in three age strata: 9–12 months, 13–18 months, and 19–23 months, and were randomly assigned (1:1:1) using block randomisation (block sizes of three and six) to one-fifth (0·1 mL), one-half (0·25 mL), or full (0·5 mL) doses of the 17DD yellow fever vaccine. Participants were followed up at 4 weeks (visit 1 [V1]), 1 year (visit 2 [V2]), and 13–48 months (visit 3 [V3]) after vaccination. The primary analysis included per-protocol participants who attended within the prespecified visit window; an intention-to-treat analysis was also conducted including all randomly assigned participants with available outcome data. Participants with missing serological data were excluded from the analysis at the corresponding visit. The primary outcome was non-inferiority in seroconversion (5 percentage-point margin) at V1 measured by 50% plaque reduction neutralisation test. This study is registered with ClinicalTrials.gov, NCT03725618, and is complete.

**Findings** Between March 26, 2019, and May 11, 2021, 1784 participants were randomly assigned to either one-fifth dose (n=600), one-half dose (n=594), or full dose (n=590). The median (IQR) age at enrolment was 13 (11–18) months. Both fractional doses met the non-inferiority criterion compared with the full dose with no difference in seroconversion between one-fifth and full doses and –0·17 (95% CI –0·52 to 0·17) difference between one-half and full doses in the per-protocol population at V1. There was no difference between the one-fifth and full doses.

**Interpretation** Both fractional doses of 17DD yellow fever vaccine were non-inferior to full doses in inducing initial seroconversion. The results support the use of fractional dose yellow fever vaccines among young children for outbreak response during supply shortages.

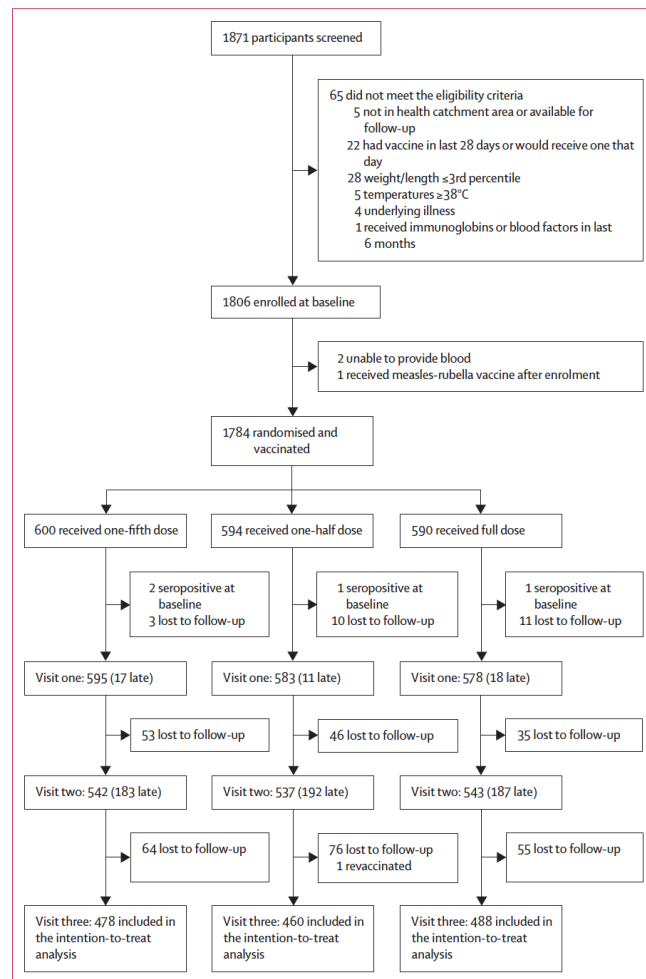


**Figure 1: Trial profile**

Some participants were excluded due to more than one criterion. Of 1756 participants who returned for visit 1 at approximately 4 weeks post-vaccination, 1710 (97.4%) met the original criteria for visit 1. Of 1622 participants who returned for visit 2 at approximately 12 months post-vaccination, 1060 (65.4%) met the original criteria for visit 2. Loss to follow-up numbers include participants who did not attend the previous visit. One participant in the one-half dose group did not seroconvert and was offered revaccination with the full dose at visit 2 and was excluded from further analysis.

|                         | All participants (N=1784) | One-fifth dose (n=600) | One-half dose (n=594) | Full dose (n=590) |
|-------------------------|---------------------------|------------------------|-----------------------|-------------------|
| Age, months*            | 13 (11–18)                | 13 (11–17)             | 13 (11–18)            | 14 (11–18)        |
| Age group, months       |                           |                        |                       |                   |
| 9–12                    | 782 (43.8%)               | 280 (46.7%)            | 260 (43.8%)           | 242 (41.0%)       |
| 13–18                   | 708 (39.7%)               | 228 (38.0%)            | 236 (39.7%)           | 244 (41.4%)       |
| 19–23                   | 294 (16.5%)               | 92 (15.3%)             | 98 (16.5%)            | 104 (17.6%)       |
| Sex                     |                           |                        |                       |                   |
| Female                  | 901 (50.5%)               | 295 (49.2%)            | 308 (51.9%)           | 298 (50.5%)       |
| Male                    | 883 (49.5%)               | 305 (50.8%)            | 286 (48.1%)           | 292 (49.5%)       |
| HIV status              |                           |                        |                       |                   |
| Positive                | 3 (0.2%)                  | 0                      | 2 (0.3%)              | 1 (0.2%)          |
| Negative                | 1781 (99.8%)              | 600 (100%)             | 592 (99.7%)           | 589 (99.8%)       |
| Serostatus at baseline† |                           |                        |                       |                   |
| Seropositive            | 4 (0.2%)                  | 2 (0.3%)               | 1 (0.2%)              | 1 (0.2%)          |
| Seronegative            | 1780 (99.8%)              | 598 (99.7%)            | 593 (99.8%)           | 589 (99.8%)       |
| Study site              |                           |                        |                       |                   |
| Kawaala                 | 649 (36.4%)               | 221 (36.8%)            | 215 (36.2%)           | 213 (36.1%)       |
| Kitebi                  | 591 (33.1%)               | 197 (32.8%)            | 198 (33.3%)           | 196 (33.2%)       |
| Nkokonjeru              | 544 (30.5%)               | 182 (30.3%)            | 181 (30.5%)           | 181 (30.7%)       |

Data are n (%) or median (IQR). \*Age at vaccination. †Seropositivity for neutralising antibodies against yellow fever virus was defined as a titre on a plaque reduction neutralisation test with a cutoff of 50% (PRNT<sub>50</sub>) or higher.

**Table 1: Trial profile of the intention-to-treat population**

|                             | Serostatus<br>(n/N)* | Serostatus (% [95% CI])* | Difference from full<br>dose (95% CI) | Geometric mean titre<br>(95% CI) | Geometric mean titre<br>ratio (95% CI)† |
|-----------------------------|----------------------|--------------------------|---------------------------------------|----------------------------------|-----------------------------------------|
| <b>All children</b>         |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=1710) |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 578/578              | 100.0% (99.3 to 100.0)   | 0‡                                    | 417 (367 to 474)                 | 0.90 (0.75 to 1.08)                     |
| One-half                    | 571/572‡             | 99.8% (99.0 to 100.0)    | -0.17 (-0.52 to 0.17)                 | 445 (388 to 511)                 | 0.96 (0.79 to 1.16)                     |
| Full                        | 560/560              | 100.0% (99.3 to 100.0)   | ..                                    | 463 (406 to 528)                 | ..                                      |
| Visit 2 (One year; n=1060)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 309/359              | 86.1% (82.1 to 89.3)     | -6.91 (-11.36 to -2.45)               | 126 (99 to 161)                  | 0.70 (0.51 to 0.96)                     |
| One-half                    | 305/345              | 88.4% (84.6 to 91.4)     | -4.57 (-8.87 to -0.28)                | 146 (115 to 184)                 | 0.81 (0.60 to 1.10)                     |
| Full                        | 331/356              | 93.0% (89.8 to 95.2)     | ..                                    | 180 (148 to 220)                 | ..                                      |
| <b>9-12 months</b>          |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=752)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 274/274              | 100.0% (98.6 to 100.0)   | 0‡                                    | 412 (337 to 504)                 | 0.93 (0.70 to 1.24)                     |
| One-half                    | 248/249              | 99.6% (97.8 to 99.9)     | -0.40 (-1.19 to 0.38)                 | 399 (321 to 497)                 | 0.90 (0.67 to 1.22)                     |
| Full                        | 229/229              | 100.0% (98.4 to 100.0)   | ..                                    | 442 (360 to 543)                 | ..                                      |
| Visit 2 (One year; n=452)   |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 135/159              | 84.9% (78.5 to 89.6)     | -9.09 (-15.83 to -2.36)               | 111 (77 to 161)                  | 0.58 (0.36 to 0.93)                     |
| One-half                    | 126/143              | 88.1% (81.8 to 92.4)     | -5.89 (-12.41 to 0.64)                | 139 (96 to 200)                  | 0.72 (0.45 to 1.15)                     |
| Full                        | 141/150              | 94.0% (89.0 to 96.8)     | ..                                    | 193 (143 to 259)                 | ..                                      |
| <b>13-18 months</b>         |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=672)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 215/215              | 100.0% (98.2 to 100.0)   | 0‡                                    | 407 (335 to 494)                 | 0.83 (0.62 to 1.10)                     |
| One-half                    | 226/226              | 100.0% (98.3 to 100.0)   | 0‡                                    | 502 (406 to 619)                 | 1.02 (0.76 to 1.37)                     |
| Full                        | 231/231              | 100.0 (98.4 to 100.0)    | ..                                    | 493 (400 to 606)                 | ..                                      |
| Visit 2 (One year; n=435)   |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 122/144              | 84.7% (78.0 to 89.7)     | -6.89 (-14.31 to 0.54)                | 115 (79 to 167)                  | 0.73 (0.45 to 1.21)                     |
| One-half                    | 131/148              | 88.5% (82.4 to 92.7)     | -3.09 (-9.95 to 3.76)                 | 153 (107 to 219)                 | 0.98 (0.61 to 1.59)                     |
| Full                        | 131/143              | 91.6% (85.9 to 95.1)     | ..                                    | 156 (113 to 215)                 | ..                                      |
| <b>19-23 months</b>         |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=286)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 89/89                | 100.0% (95.9 to 100.0)   | 0‡                                    | 458 (331 to 633)                 | 1.02 (0.65 to 1.59)                     |
| One-half                    | 97/97                | 100.0% (96.2 to 100.0)   | 0‡                                    | 430 (312 to 592)                 | 0.96 (0.61 to 1.49)                     |
| Full                        | 100/100              | 100.0% (96.3 to 100.0)   | ..                                    | 450 (332 to 610)                 | ..                                      |
| Visit 2 (One year; n=173)   |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 52/56                | 92.9% (83.0 to 97.2)     | -0.79 (-9.84 to 8.25)                 | 234 (134 to 410)                 | 1.10 (0.53 to 2.30)                     |
| One-half                    | 48/54                | 88.9% (77.8 to 94.8)     | -4.76 (-15.08 to 5.56)                | 145 (83 to 252)                  | 0.68 (0.33 to 1.42)                     |
| Full                        | 59/63                | 93.7% (84.8 to 97.5)     | ..                                    | 212 (132 to 342)                 | ..                                      |
| <b>Females</b>              |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=860)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 286/286              | 100.0% (98.7 to 100.0)   | 0‡                                    | 404 (337 to 483)                 | 0.84 (0.65 to 1.08)                     |
| One-half                    | 295/295              | 100.0% (98.7 to 100.0)   | 0‡                                    | 460 (385 to 549)                 | 0.96 (0.75 to 1.23)                     |
| Full                        | 279/279              | 100.0% (98.6 to 100.0)   | ..                                    | 479 (402 to 572)                 | ..                                      |
| Visit 2 (One year; n=544)   |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 158/185              | 85.4% (79.6 to 89.8)     | -7.64 (-13.90 to -1.38)               | 122 (87 to 171)                  | 0.70 (0.45 to 1.08)                     |
| One-half                    | 158/172              | 91.9% (86.8 to 95.1)     | -1.19 (-6.66 to 4.29)                 | 182 (134 to 249)                 | 1.05 (0.69 to 1.58)                     |
| Full                        | 174/187              | 93.1% (88.5 to 95.9)     | ..                                    | 174 (133 to 228)                 | ..                                      |

(Table 2 continues on next page)

|                             | Serostatus<br>(n/N)* | Serostatus (% [95% CI])* | Difference from full<br>dose (95% CI) | Geometric mean titre<br>(95% CI) | Geometric mean titre<br>ratio (95% CI)† |
|-----------------------------|----------------------|--------------------------|---------------------------------------|----------------------------------|-----------------------------------------|
| <b>All children</b>         |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=1710) |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 578/578              | 100.0% (99.3 to 100.0)   | 0‡                                    | 417 (367 to 474)                 | 0.90 (0.75 to 1.08)                     |
| One-half                    | 571/572‡             | 99.8% (99.0 to 100.0)    | -0.17 (-0.52 to 0.17)                 | 445 (388 to 511)                 | 0.96 (0.79 to 1.16)                     |
| Full                        | 560/560              | 100.0% (99.3 to 100.0)   | ..                                    | 463 (406 to 528)                 | ..                                      |
| Visit 2 (One year; n=1060)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 309/359              | 86.1% (82.1 to 89.3)     | -6.91 (-11.36 to -2.45)               | 126 (99 to 161)                  | 0.70 (0.51 to 0.96)                     |
| One-half                    | 305/345              | 88.4% (84.6 to 91.4)     | -4.57 (-8.87 to -0.28)                | 146 (115 to 184)                 | 0.81 (0.60 to 1.10)                     |
| Full                        | 331/356              | 93.0% (89.8 to 95.2)     | ..                                    | 180 (148 to 220)                 | ..                                      |
| <b>9-12 months</b>          |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=752)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 274/274              | 100.0% (98.6 to 100.0)   | 0‡                                    | 412 (337 to 504)                 | 0.93 (0.70 to 1.24)                     |
| One-half                    | 248/249              | 99.6% (97.8 to 99.9)     | -0.40 (-1.19 to 0.38)                 | 399 (321 to 497)                 | 0.90 (0.67 to 1.22)                     |
| Full                        | 229/229              | 100.0% (98.4 to 100.0)   | ..                                    | 442 (360 to 543)                 | ..                                      |
| Visit 2 (One year; n=452)   |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 135/159              | 84.9% (78.5 to 89.6)     | -9.09 (-15.83 to -2.36)               | 111 (77 to 161)                  | 0.58 (0.36 to 0.93)                     |
| One-half                    | 126/143              | 88.1% (81.8 to 92.4)     | -5.89 (-12.41 to 0.64)                | 139 (96 to 200)                  | 0.72 (0.45 to 1.15)                     |
| Full                        | 141/150              | 94.0% (89.0 to 96.8)     | ..                                    | 193 (143 to 259)                 | ..                                      |
| <b>13-18 months</b>         |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=672)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 215/215              | 100.0% (98.2 to 100.0)   | 0‡                                    | 407 (335 to 494)                 | 0.83 (0.62 to 1.10)                     |
| One-half                    | 226/226              | 100.0% (98.3 to 100.0)   | 0‡                                    | 502 (406 to 619)                 | 1.02 (0.76 to 1.37)                     |
| Full                        | 231/231              | 100.0 (98.4 to 100.0)    | ..                                    | 493 (400 to 606)                 | ..                                      |
| Visit 2 (One year; n=435)   |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 122/144              | 84.7% (78.0 to 89.7)     | -6.89 (-14.31 to 0.54)                | 115 (79 to 167)                  | 0.73 (0.45 to 1.21)                     |
| One-half                    | 131/148              | 88.5% (82.4 to 92.7)     | -3.09 (-9.95 to 3.76)                 | 153 (107 to 219)                 | 0.98 (0.61 to 1.59)                     |
| Full                        | 131/143              | 91.6% (85.9 to 95.1)     | ..                                    | 156 (113 to 215)                 | ..                                      |
| <b>19-23 months</b>         |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=286)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 89/89                | 100.0% (95.9 to 100.0)   | 0‡                                    | 458 (331 to 633)                 | 1.02 (0.65 to 1.59)                     |
| One-half                    | 97/97                | 100.0% (96.2 to 100.0)   | 0‡                                    | 430 (312 to 592)                 | 0.96 (0.61 to 1.49)                     |
| Full                        | 100/100              | 100.0% (96.3 to 100.0)   | ..                                    | 450 (332 to 610)                 | ..                                      |
| Visit 2 (One year; n=173)   |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 52/56                | 92.9% (83.0 to 97.2)     | -0.79 (-9.84 to 8.25)                 | 234 (134 to 410)                 | 1.10 (0.53 to 2.30)                     |
| One-half                    | 48/54                | 88.9% (77.8 to 94.8)     | -4.76 (-15.08 to 5.56)                | 145 (83 to 252)                  | 0.68 (0.33 to 1.42)                     |
| Full                        | 59/63                | 93.7% (84.8 to 97.5)     | ..                                    | 212 (132 to 342)                 | ..                                      |
| <b>Females</b>              |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=860)  |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 286/286              | 100.0% (98.7 to 100.0)   | 0‡                                    | 404 (337 to 483)                 | 0.84 (0.65 to 1.08)                     |
| One-half                    | 295/295              | 100.0% (98.7 to 100.0)   | 0‡                                    | 460 (385 to 549)                 | 0.96 (0.75 to 1.23)                     |
| Full                        | 279/279              | 100.0% (98.6 to 100.0)   | ..                                    | 479 (402 to 572)                 | ..                                      |
| Visit 2 (One year; n=544)   |                      |                          |                                       |                                  |                                         |
| One-fifth                   | 158/185              | 85.4% (79.6 to 89.8)     | -7.64 (-13.90 to -1.38)               | 122 (87 to 171)                  | 0.70 (0.45 to 1.08)                     |
| One-half                    | 158/172              | 91.9% (86.8 to 95.1)     | -1.19 (-6.66 to 4.29)                 | 182 (134 to 249)                 | 1.05 (0.69 to 1.58)                     |
| Full                        | 174/187              | 93.1% (88.5 to 95.9)     | ..                                    | 174 (133 to 228)                 | ..                                      |

(Table 2 continues on next page)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Serostatus<br>(n/N)* | Serostatus (% [95% CI])* | Difference from full<br>dose (95% CI) | Geometric mean titre<br>(95% CI) | Geometric mean titre<br>ratio (95% CI)† |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|--------------------------|---------------------------------------|----------------------------------|-----------------------------------------|
| (Continued from previous page)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                      |                          |                                       |                                  |                                         |
| <b>Males</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                      |                          |                                       |                                  |                                         |
| Visit 1 (One month; n=850)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                      |                          |                                       |                                  |                                         |
| One-fifth                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 292/292              | 100.0% (98.7 to 100.0)   | 0‡                                    | 431 (359 to 518)                 | 0.97 (0.74 to 1.27)                     |
| One-half                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 276/277              | 99.6% (98.0 to 99.9)     | -0.36 (-1.07 to 0.35)                 | 432 (350 to 533)                 | 0.97 (0.73 to 1.29)                     |
| Full                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 281/281              | 100.0% (98.7 to 100.0)   | ..                                    | 446 (366 to 543)                 | ..                                      |
| Visit 2 (One year; n=516)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                      |                          |                                       |                                  |                                         |
| One-fifth                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 151/174              | 86.8% (81.0 to 91.0)     | -6.12 (-12.47 to 0.68)                | 131 (93 to 185)                  | 0.70 (0.45 to 1.10)                     |
| One-half                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 147/173              | 85.0% (78.9 to 89.5)     | -7.93 (-14.51 to -1.34)               | 116 (83 to 164)                  | 0.62 (0.40 to 0.98)                     |
| Full                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 157/169              | 92.9% (88.0 to 95.9)     | ..                                    | 187 (139 to 251)                 | ..                                      |
| For the per-protocol analyses, participants were required to have Visit 2 completed within the originally prespecified window (365–395 days post-vaccination); participants with delayed visit 2 assessments outside this window were excluded from the per-protocol visit 2 analyses, but were included in intention-to-treat analyses. *Includes participants who seroconverted at visit 1 and those who were seropositive (PRNT <sub>50</sub> ≥ 10) at visit 2. †Analysis of geometric mean titres were descriptive; geometric mean titre ratio=fractional/standard. ‡No confidence interval because difference is zero. §The participant who did not seroconvert was a male in the 9–12-month age group, HIV negative, and yellow fever seronegative at baseline, from the Nkokonjeru study site. |                      |                          |                                       |                                  |                                         |
| <b>Table 2: Seropositivity and geometric mean titres measured by plaque reduction neutralisation test with 50% cutoff (PRNT<sub>50</sub>) in the per-protocol population</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                      |                          |                                       |                                  |                                         |

|                                                                                                                                                                                               | One-fifth versus full |                                         | One-half versus full |                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-----------------------------------------|----------------------|-----------------------------------------|
|                                                                                                                                                                                               | Difference            | Two-sided<br>90% CI<br>(lower<br>bound) | Difference           | Two-sided<br>90% CI<br>(lower<br>bound) |
| <b>Visit 1 (One month)</b>                                                                                                                                                                    |                       |                                         |                      |                                         |
| All                                                                                                                                                                                           | 0                     | ..                                      | -0.17%               | -0.46%                                  |
| 9–12 months                                                                                                                                                                                   | 0                     | ..                                      | -0.40%               | -1.06%                                  |
| 13–18 months                                                                                                                                                                                  | 0                     | ..                                      | 0                    | ..                                      |
| 19–23 months                                                                                                                                                                                  | 0                     | ..                                      | 0                    | ..                                      |
| Female                                                                                                                                                                                        | 0                     | ..                                      | 0                    | ..                                      |
| Male                                                                                                                                                                                          | 0                     | ..                                      | -0.36%               | -0.95%                                  |
| <b>Visit 2 (One year)</b>                                                                                                                                                                     |                       |                                         |                      |                                         |
| All                                                                                                                                                                                           | -6.91%                | -10.65%                                 | -4.57%               | -8.18%                                  |
| 9–12 months                                                                                                                                                                                   | -9.09%                | -14.75%                                 | -5.89%               | -11.36%                                 |
| 13–18 months                                                                                                                                                                                  | -6.89%                | -13.12%                                 | -3.09%               | -8.85%                                  |
| 19–23 months                                                                                                                                                                                  | -7.90%                | -8.38%                                  | -4.76%               | -13.42%                                 |
| Female                                                                                                                                                                                        | -7.64%                | -12.90%                                 | -1.19%               | -5.78%                                  |
| Male                                                                                                                                                                                          | 6.12%                 | -11.45%                                 | -7.93%               | -7.93%                                  |
| Non-inferiority was concluded if the lower bound of the 90% confidence interval exceeded the prespecified non-inferiority margin of -5%.                                                      |                       |                                         |                      |                                         |
| <b>Table 3: Non-inferiority test and the difference in seropositivity measured by plaque reduction neutralisation test with 50% cutoff (PRNT<sub>50</sub>) in the per-protocol population</b> |                       |                                         |                      |                                         |



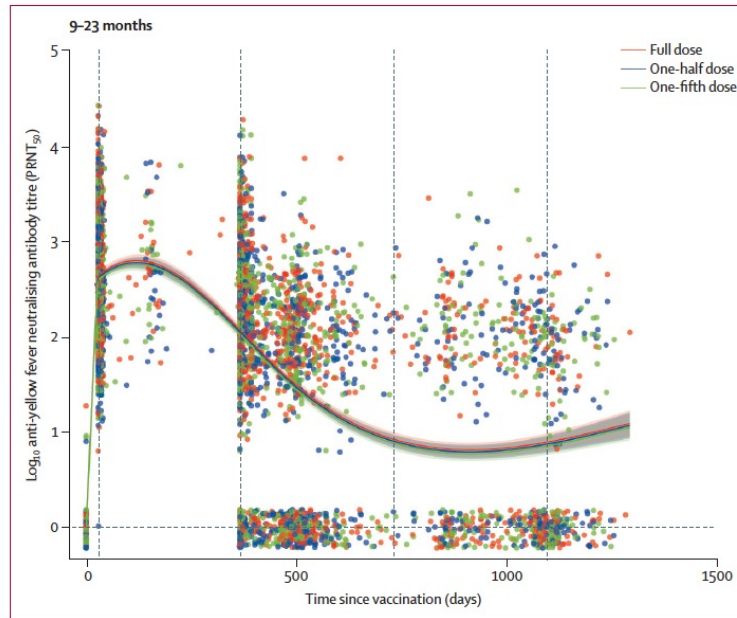
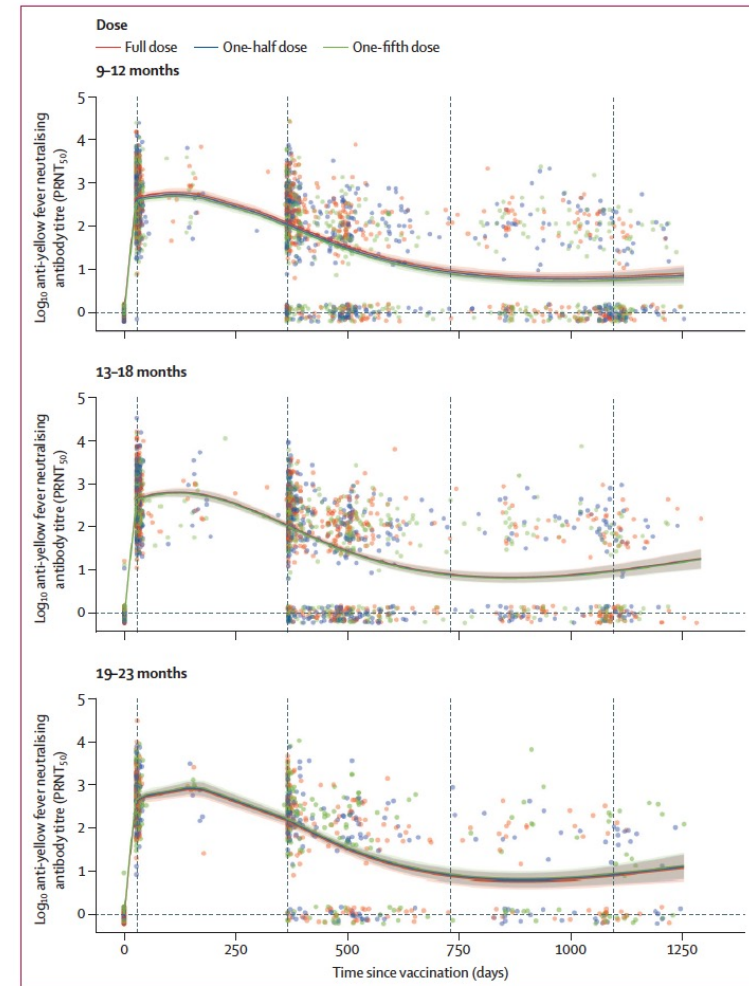


**Figure 2:** Distribution of NAb titres against yellow fever measured as  $\log_{10}$  PRNT<sub>50</sub> values over time (days since vaccination) in the intention-to-treat population of children aged 9-23 months. The coloured circles represent the observed NAb titres for the different doses. Solid lines represent the predicted NAb titres for the different doses. The horizontal black dotted line represents the threshold for assay positivity ( $\log_{10}$  [PRNT<sub>50</sub>]=0). Vertical dash-dotted line indicates 28, 365, 730, and 1095-day follow-up points. Shaded areas represent the 95% CI. The centre for the confidence interval is the predicted (mean) values. NAb=neutralising antibodies. PRNT<sub>50</sub>=50% plaque reduction neutralisation test.





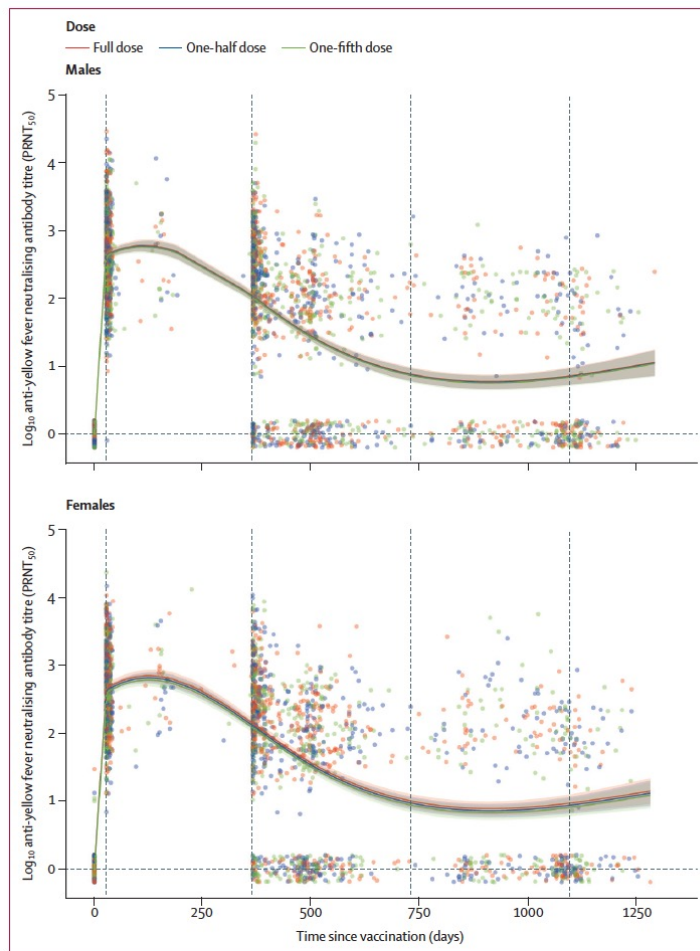


**Figure 3:** Distribution of NAb titres against yellow fever measured as  $\log_{10}$  PRNT<sub>50</sub> values over time (days since vaccination) in the intention-to-treat population of children aged 9-23 months, by age group and sex. The coloured circles represent the observed NAb titres for the different doses. Solid lines represent the predicted NAb titres for the different doses. The horizontal black dotted line represents the threshold for assay positivity ( $\log_{10}$  [PRNT<sub>50</sub>]=0). Vertical dash-dotted lines indicate the 28, 365, 730, and 1095-day follow-up points. Shaded areas represent the 95% CI. The centre for the confidence interval is the predicted (mean) values. NABs=neutralising antibodies. PRNT<sub>50</sub>=50% plaque reduction neutralisation test.

### Implications of all the available evidence

These findings support the use of fractional dosing of 17DD yellow fever vaccine among young children for outbreak response, providing additional evidence of optimal fractional dosing and duration of immunological response. Studies further assessing long-term protection are needed.

**Fibrodysplasia ossificans progressiva (FOP)** (auch *Münchmeyer-Syndrom*) ist eine extrem seltene, schwere genetische Erkrankung des Bindegewebes.

### Was passiert bei FOP?

- **Verknöcherung des Gewebes:** Skelettmuskeln, Sehnen, Bänder und Faszien wandeln sich schrittweise und dauerhaft in echtes Knochengewebe um („zweites Skelett“).
- **Verlust der Beweglichkeit:** Gelenke versteifen (Ankylose), wodurch alltägliche Bewegungen nach und nach unmöglich werden.
- **Typisches Kennzeichen bei Geburt:** Bei fast allen Betroffenen sind die Großzehen auffällig verkümmert oder schief (*Hallux valgus*, Fehlbildung der ersten Zehe).
- **Verlauf:** In Schüben (*Flare-ups*) – oft ausgelöst durch Stürze, Infektionen, Operationen oder auch spontan – entstehen schmerzhafte Schwellungen, die später verknöchern.]
- **Lebensgefahr:** Durch die Verknöcherung des Brustkorbs wird im fortgeschrittenen Stadium oft die Atemmuskulatur eingeschränkt.

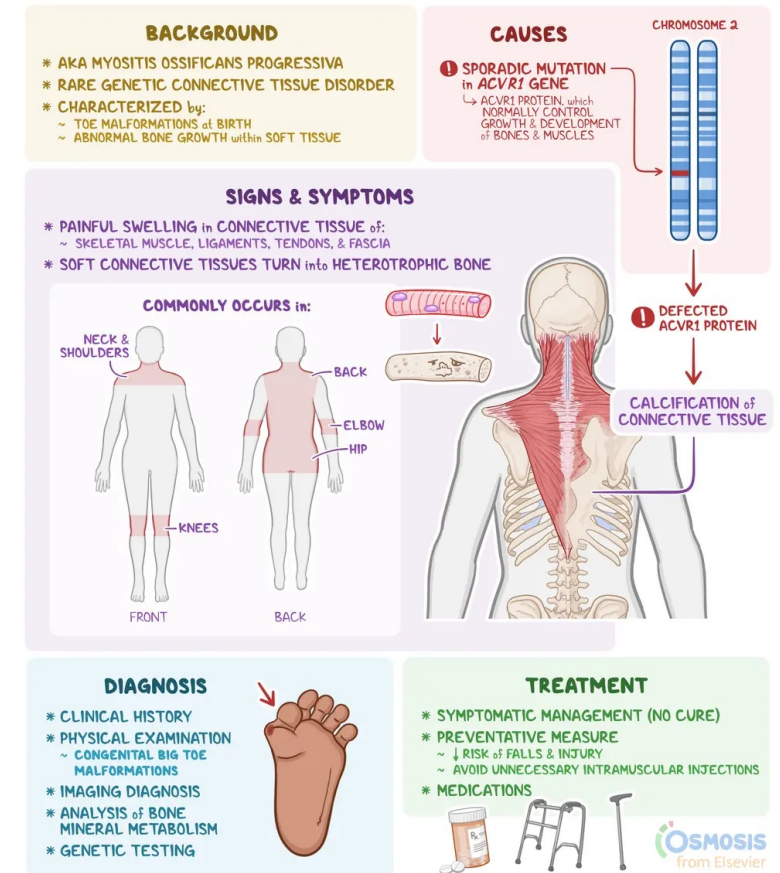


## Ursache und Diagnose

- **Genetik:** Ursache ist eine aktivierende Mutation im **ACVR1-Gen** (auch **ALK2-Gen** genannt) auf Chromosom 2q24.1.
- **Häufigkeit:** Die Erkrankung betrifft weltweit schätzungsweise nur rund 600 bis 800 bekannte Fälle (ca. 1 zu 2 Millionen Menschen).
- **Diagnose:** Die Diagnose wird durch den klinischen Befund (Großzehen-Fehlbildung + schmerzhaftes Schwellungen) und eine anschließende **genetische Untersuchung** gesichert.

## Behandlung und wichtige Vorsichtsmaßnahmen

- **Keine Heilung:** Es gibt bislang keine ursächliche Heilung.
- **Wichtiger Hinweis zu Operationen:** Operative Eingriffe zur Entfernung des neuen Knochens sowie Muskelbiopsien oder intramuskuläre Injektionen sind **kontraindiziert** (streng verboten), da das Trauma den Körper zu noch massiverer neuer Knochenbildung anregt.
- **Medikamente:** Akute Schübe werden oft mit Kortikosteroiden behandelt; spezifische Therapien sind je nach Land unterschiedlich zugelassen (in der EU beispielsweise ist Palovaroten nicht von der EMA zugelassen, während es andernorts geprüft wurde).

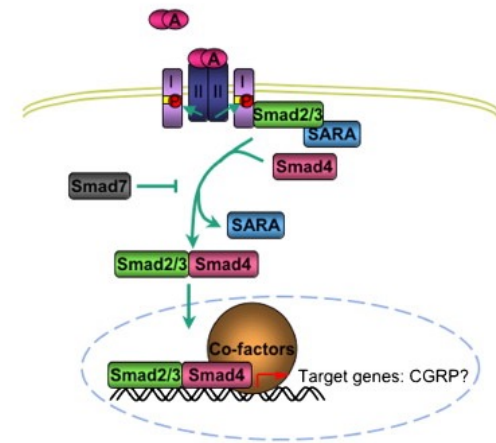


**Aktivin A** ist ein dimeres Proteohormon und Wachstumsfaktor aus der TGF- $\beta$ -Superfamilie, das an spezifische Aktivin-Rezeptoren (wie ActRIIA) bindet und über SMAD2/3-Proteine signalisiert.

### Grundlegende Eigenschaften und Bildung

- **Struktur:** Besteht aus zwei identischen  $\beta$ A-Untereinheiten (Homodimer).
- **Bildungsorte:** Unter anderem in den Granulosazellen der Ovarien, Sertoli-Zellen der Hoden, der Hypophyse, der Plazenta und weiteren Geweben.
- **Gegenspieler:** Wirkt biologisch als Antagonist zu **Inhibin**.

A



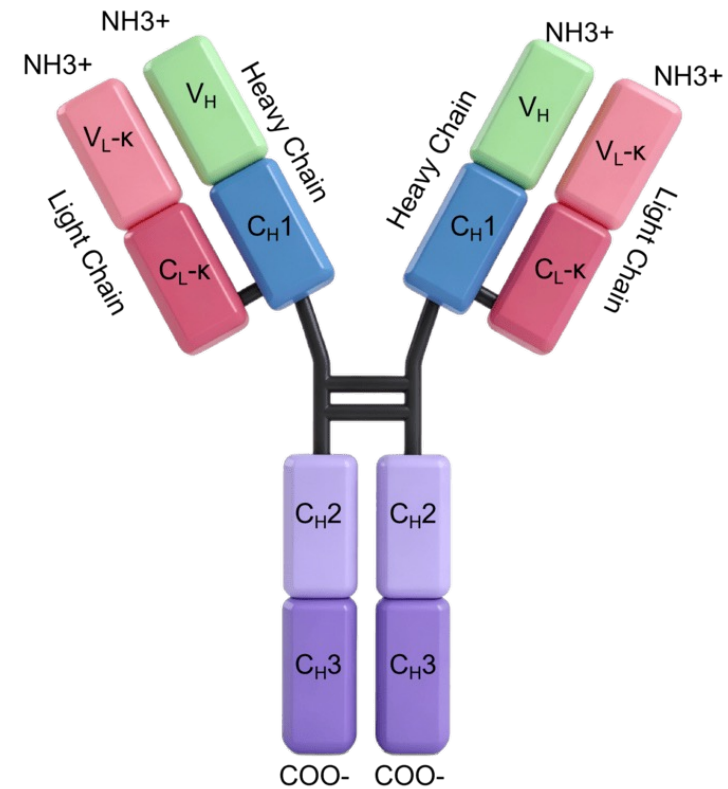
B

| Ligands                              | Type I receptor                                | Type II receptor               | R-Smad      | C-Smad | I-Smad   |
|--------------------------------------|------------------------------------------------|--------------------------------|-------------|--------|----------|
| Activin A                            | ALK4 (ActRIB)                                  | ActRII(A)<br>ActRIIB           | Smad2, 3    | Smad4  | Smad7    |
| BMP-2, 4, 7                          | ALK2 (ActRI)<br>ALK3 (BMPRIA)<br>ALK6 (BMPRIB) | ActRII(A)<br>ActRIIB<br>BMPRII | Smad1, 5, 8 | Smad4  | Smad6, 7 |
| TGF- $\beta$ 1, $\beta$ 2, $\beta$ 3 | ALK5 (TGF $\beta$ RI)<br>ALK1 (TSR1)           | TGF $\beta$ RII                | Smad2, 3    | Smad4  | Smad7    |

**Garetosmab** (Handelsname **Pasatru™**) ist ein vollständig humaner monoklonaler Antikörper (Isotyp IgG4), der im August 2026 von der US-amerikanischen Zulassungsbehörde FDA zugelassen wurde. Entwickelt von Regeneron Pharmaceuticals, dient das Medikament zur Behandlung der extrem seltenen und schweren genetischen Knochenerkrankung **Fibrodysplasia ossificans progressiva (FOP)**

FOP wird durch eine Mutation im *ACVR1*-Gen verursacht. Bei gesunden Menschen fungiert das Protein **Activin A** als Ausschalter für diesen Rezeptor. Bei FOP-Patienten führt Activin A jedoch dazu, dass der mutierte Rezeptor dauerhaft aktiviert wird, was zu einer unkontrollierten Umwandlung von Muskel- und Bindegewebe in Knochen (heterotope Ossifikation, kurz HO) führt

- Garetosmab bindet gezielt an **Activin A** und blockiert dessen Aktivität.
- Dadurch wird die fehlerhafte Signalübertragung gestoppt und die Entstehung neuer, **abnormaler Knochenwucherungen sowie entzündlicher Schübe (Flare-ups)** drastisch reduziert.





# Efficacy and safety of garetosmab, an activin A-blocking antibody, in fibrodysplasia ossificans progressiva (OPTIMA): a randomised, double-blind, placebo-controlled, phase 3 trial

## Summary

**Background** Fibrodysplasia ossificans progressiva (FOP) is an ultrarare genetic disorder resulting in progressive heterotopic ossification of ligaments, tendons, and muscles, leading to disability and early mortality. FOP is caused by heterozygous gain-of-function mutations in the activin receptor type 1A, allowing this receptor to be aberrantly activated by activin A (ActA), which normally inhibits this receptor, thus driving heterotopic bone formation. In preclinical models and an earlier phase 2 trial (LUMINA-1) in FOP, an antibody blocking ActA (garetosmab) prevented heterotopic ossification. We aimed to evaluate the efficacy and safety of garetosmab in adults living with FOP.

**Methods** OPTIMA is a randomised, double-blind, placebo-controlled, phase 3 trial conducted at 18 study sites across 16 countries and regions. Participants aged 18 years or older with FOP were randomly assigned (1:1:1) to monthly intravenous placebo, garetosmab 3 mg/kg, or garetosmab 10 mg/kg. Randomisation was stratified by baseline Cumulative Analogue Joint Involvement Scale score and previous participation in the LUMINA-1 study. The primary efficacy and safety endpoints were total number of new heterotopic bone lesions at week 56 and treatment-emergent adverse events of special interest (AESIs) through week 56, analysed in all randomised participants who received at least one dose of the study drug. This trial is registered with ClinicalTrials.gov (NCT05394116); the trial is active (completed primary endpoint) but not recruiting participants.

**Findings** Between Nov 21, 2022, and July 4, 2024, 63 participants were enrolled and randomly assigned (placebo, n=21; garetosmab 3 mg/kg, n=19; garetosmab 10 mg/kg, n=23). The mean age was 26·6 years (SD 6·8); 38 (60%) participants were female and 25 (40%) male. 62 participants completed 56 weeks of treatment; one participant in the placebo group discontinued at 53 weeks. The total number of new heterotopic bone lesions was significantly lower with garetosmab: there were 19 lesions with placebo versus one lesion with garetosmab 3 mg/kg (rate ratio *vs* placebo: 0·06 [95% CI 0·00–0·73]; *p*=0·027) and two lesions with garetosmab 10 mg/kg (rate ratio *vs* placebo: 0·10 [0·01–0·76]; *p*=0·026). Treatment-emergent AESIs occurred in one (5%) of 21 participants receiving placebo, zero of 19 receiving garetosmab 3 mg/kg, and four (17%) of 23 receiving garetosmab 10 mg/kg; all were considered treatment-related. No deaths occurred.

**Interpretation** Garetosmab substantially reduced the number of new heterotopic bone lesions, providing robust evidence of its potential to be an efficacious and generally well tolerated disease-modifying therapy for FOP.

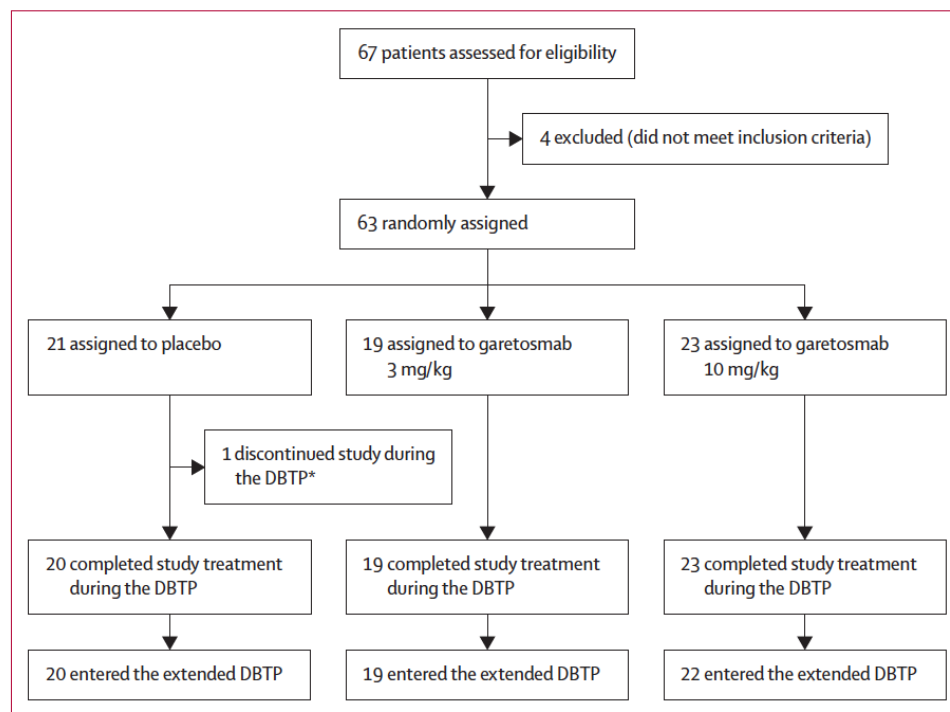


**Figure 1: Trial profile**

DBTP=double-blind treatment period. \*Discontinued at week 53 due to a serious adverse event of ovarian cyst deemed unrelated to the study drug.

|                                                                | Placebo<br>(n=21) | Garetosmab<br>3 mg/kg<br>(n=19) | Garetosmab<br>10 mg/kg<br>(n=23) | Total (N=63) |
|----------------------------------------------------------------|-------------------|---------------------------------|----------------------------------|--------------|
| Age, years                                                     | 29.3 (7.3)        | 24.6 (6.0)                      | 25.7 (6.3)                       | 26.6 (6.8)   |
| Sex                                                            |                   |                                 |                                  |              |
| Female                                                         | 11 (52%)          | 12 (63%)                        | 15 (65%)                         | 38 (60%)     |
| Male                                                           | 10 (48%)          | 7 (37%)                         | 8 (35%)                          | 25 (40%)     |
| Ethnicity                                                      |                   |                                 |                                  |              |
| Hispanic or Latino                                             | 5 (24%)           | 2 (11%)                         | 5 (22%)                          | 12 (19%)     |
| Not Hispanic or Latino                                         | 15 (71%)          | 15 (79%)                        | 18 (78%)                         | 48 (76%)     |
| Unknown                                                        | 1 (5%)            | 2 (11%)                         | 0                                | 3 (5%)       |
| Race                                                           |                   |                                 |                                  |              |
| White                                                          | 13 (62%)          | 11 (58%)                        | 18 (78%)                         | 42 (67%)     |
| Asian                                                          | 7 (33%)           | 8 (42%)                         | 4 (17%)                          | 19 (30%)     |
| Black or African American                                      | 0                 | 0                               | 1 (4%)                           | 1 (2%)       |
| Unknown                                                        | 1 (5%)            | 0                               | 0                                | 1 (2%)       |
| Weight, kg                                                     | 61.3 (14.2)       | 56.1 (15.6)                     | 60.0 (16.3)                      | 59.3 (15.3)  |
| BMI, kg/m <sup>2</sup>                                         | 22.8 (4.6)        | 20.5 (4.8)                      | 23.8 (6.7)                       | 22.5 (5.6)   |
| Duration of FOP disease, years                                 | 26.8 (8.6)        | 22.0 (9.4)                      | 25.2 (6.7)                       | 24.8 (8.3)   |
| Previous medications                                           |                   |                                 |                                  |              |
| Analgesics                                                     | 4 (19%)           | 4 (21%)                         | 1 (4%)                           | 9 (14%)      |
| Anti-inflammatory and antirheumatic products                   | 3 (14%)           | 2 (11%)                         | 1 (4%)                           | 6 (10%)      |
| Diagnosis findings                                             |                   |                                 |                                  |              |
| Physical examination                                           |                   |                                 |                                  |              |
| Malformation of great toes                                     | 18 (86%)          | 16 (84%)                        | 23 (100%)                        | 57 (90%)     |
| Malformation of thumbs                                         | 9 (43%)           | 3 (16%)                         | 9 (39%)                          | 21 (33%)     |
| Presence of heterotopic bone lesions                           | 19 (90%)          | 17 (89%)                        | 20 (87%)                         | 56 (89%)     |
| Osteochondroma                                                 | 11 (52%)          | 7 (37%)                         | 12 (52%)                         | 30 (48%)     |
| Soft tissue swelling                                           | 14 (67%)          | 9 (47%)                         | 7 (30%)                          | 30 (48%)     |
| Stiff neck                                                     | 15 (71%)          | 16 (84%)                        | 18 (78%)                         | 49 (78%)     |
| Absence of crawling                                            | 5 (24%)           | 2 (11%)                         | 3 (13%)                          | 10 (16%)     |
| Flare-up signs and symptoms                                    | 12 (57%)          | 7 (37%)                         | 8 (35%)                          | 27 (43%)     |
| FOP genetic variant                                            |                   |                                 |                                  |              |
| R206H (classic)                                                | 20 (95%)          | 17 (89%)                        | 23 (100%)                        | 60 (95%)     |
| Other*                                                         | 1 (5%)            | 2 (11%)                         | 0                                | 3 (5%)       |
| Participated in the LUMINA-1 study                             | 5 (24%)           | 3 (16%)                         | 6 (26%)                          | 14 (22%)     |
| Number of participant-reported flare-ups in previous 12 months | 2.9 (2.6)         | 5.5 (12.1)                      | 2.4 (3.0)                        | 3.5 (7.0)    |
| Total CAJIS score                                              | 13.3 (3.9)        | 11.4 (4.7)                      | 12.6 (4.3)                       | 12.5 (4.3)   |

Data are mean (SD) or n (%). CAJIS=Cumulative Analogue Joint Involvement Scale. FOP=fibrodysplasia ossificans progressiva. \*Based on confirmatory genetic testing, two variants (R258S, Q207E) were reported in three participants (data on file).

**Table 1: Baseline demographic and clinical characteristics**

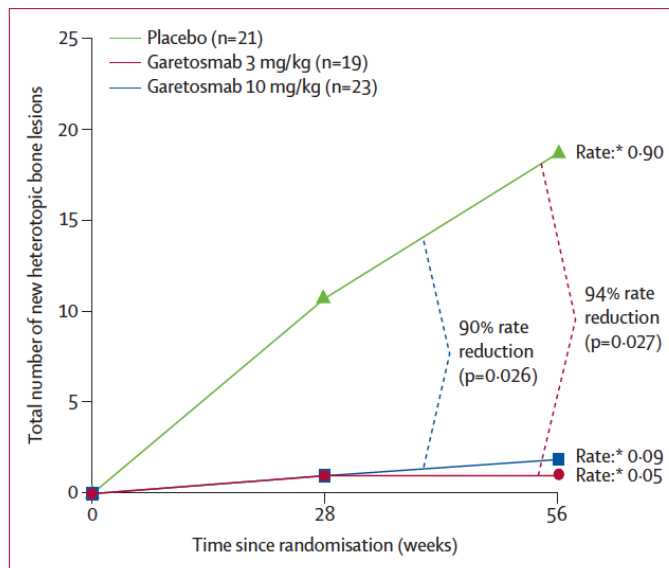


**Figure 2:** Total number of new heterotopic bone lesions at week 56  
Rate ratio versus placebo for the garetosmab 3 mg/kg group: 0.06 (95% CI 0.00-0.73);  $p=0.027$ . Rate ratio versus placebo for the garetosmab 10 mg/kg group: 0.10 (0.01-0.76);  $p=0.026$ . \*Rate is defined as the number of new heterotopic bone lesions divided by the sample size.

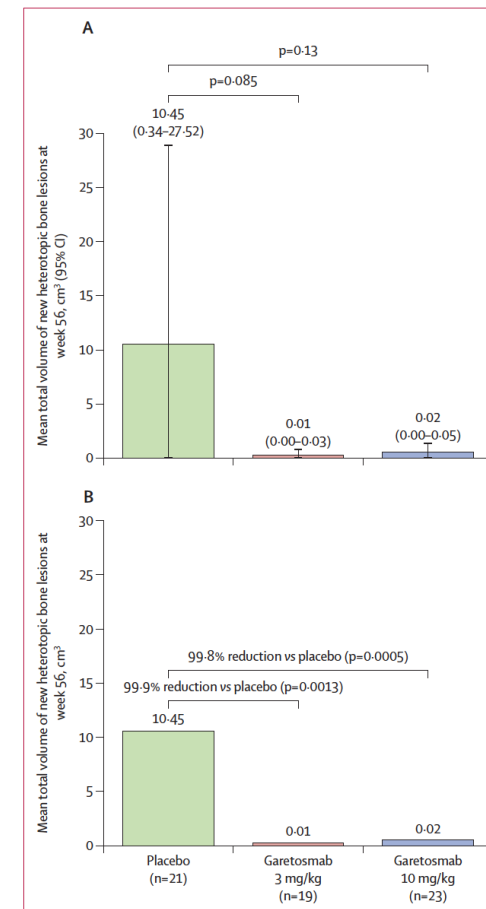


**Figure 3:** Total volume of new heterotopic bone lesions for participants with new heterotopic bone lesions at week 56 based on the predefined analysis (A), and based on a post-hoc analysis using the Tweedie distribution (B). As the reduction in lesion volume was 99.9% for garetosmab 3 mg/kg and 99.8% for garetosmab 10 mg/kg, compared with placebo, a post-hoc analysis using a generalised linear model using the Tweedie distribution (which captures both the frequency and volume of new lesions) was performed. For garetosmab 3 mg/kg, difference versus placebo was 99.9% (95% CI 98.3-100);  $p=0.0013$ . For garetosmab 10 mg/kg, difference versus placebo was 99.8% (96.4-100);  $p=0.0005$ .

|                                                                                               | Placebo (n=21) | Garetosmab<br>3 mg/kg (n=19) | Garetosmab<br>10 mg/kg (n=23) |
|-----------------------------------------------------------------------------------------------|----------------|------------------------------|-------------------------------|
| <b>Treatment-emergent AESIs</b>                                                               |                |                              |                               |
| Any treatment-emergent AESIs                                                                  | 1 (5%)         | 0                            | 4 (17%)                       |
| Severe treatment-emergent AESIs                                                               | 0              | 0                            | 0                             |
| Treatment-emergent serious AESIs                                                              | 0              | 0                            | 1 (4%)                        |
| Treatment-related treatment-emergent AESIs                                                    | 1 (5%)         | 0                            | 4 (17%)                       |
| Treatment-emergent AESIs leading to treatment discontinuation                                 | 0              | 0                            | 0                             |
| Treatment-emergent AESIs leading to death                                                     | 0              | 0                            | 0                             |
| <b>TEAEs</b>                                                                                  |                |                              |                               |
| Any TEAE                                                                                      | 21 (100%)      | 18 (95%)                     | 23 (100%)                     |
| Severe TEAEs                                                                                  | 2 (10%)        | 1 (5%)                       | 1 (4%)                        |
| Treatment-emergent SAEs                                                                       | 2 (10%)        | 1 (5%)                       | 2 (9%)                        |
| Treatment-related TEAEs                                                                       | 13 (62%)       | 16 (84%)                     | 21 (91%)                      |
| TEAEs leading to treatment discontinuation                                                    | 1 (5%)*        | 0                            | 0                             |
| TEAEs leading to death                                                                        | 0              | 0                            | 0                             |
| <b>TEAEs by preferred term occurring in at least four participants in any treatment group</b> |                |                              |                               |
| Epistaxis                                                                                     | 5 (24%)        | 10 (53%)                     | 4 (17%)                       |
| Arthralgia                                                                                    | 9 (43%)        | 5 (26%)                      | 4 (17%)                       |
| Nasopharyngitis                                                                               | 5 (24%)        | 5 (26%)                      | 1 (4%)                        |
| Rash                                                                                          | 0              | 5 (26%)                      | 1 (4%)                        |
| FOP flare-up                                                                                  | 5 (24%)        | 4 (21%)                      | 2 (9%)                        |
| Musculoskeletal chest pain                                                                    | 1 (5%)         | 4 (21%)                      | 0                             |
| Madarosis                                                                                     | 4 (19%)        | 3 (16%)                      | 6 (26%)                       |
| Acne                                                                                          | 2 (10%)        | 3 (16%)                      | 7 (30%)                       |
| Headache                                                                                      | 4 (19%)        | 3 (16%)                      | 4 (17%)                       |
| Pain in extremity                                                                             | 8 (38%)        | 2 (11%)                      | 0                             |
| Influenza                                                                                     | 4 (19%)        | 2 (11%)                      | 3 (13%)                       |
| Nausea                                                                                        | 4 (19%)        | 2 (11%)                      | 2 (9%)                        |
| Back pain                                                                                     | 6 (29%)        | 1 (5%)                       | 1 (4%)                        |
| Alopecia                                                                                      | 4 (19%)        | 1 (5%)                       | 1 (4%)                        |
| Musculoskeletal pain                                                                          | 5 (24%)        | 1 (5%)                       | 0                             |
| Fall                                                                                          | 4 (19%)        | 1 (5%)                       | 0                             |
| <b>TEAEs by severity†</b>                                                                     |                |                              |                               |
| Mild                                                                                          | 9 (43%)        | 8 (42%)                      | 9 (39%)                       |
| Moderate                                                                                      | 10 (48%)       | 9 (47%)                      | 13 (57%)                      |
| Severe                                                                                        | 2 (10%)        | 1 (5%)                       | 1 (4%)                        |

Data are n (%). AESI=adverse event of special interest. FOP=fibrodysplasia ossificans progressiva. SAE=serious adverse event. TEAE=treatment-emergent adverse event. \* Ovarian cyst. †If a participant had an event with more than one occurrence with multiple severity levels, the most severe occurrence was reported.

**Table 2: Summary of safety during the double-blind treatment period (safety set)**

### Implications of all the available evidence

The findings from this phase 3 OPTIMA trial, together with those from the earlier phase 2 LUMINA-1 trial, provide strong evidence supporting the efficacy and safety of garetosmab in adults with FOP. Given that garetosmab prevents new heterotopic bone formation, stops radiological disease progression, and lowers clinician-reported flare-ups, and is balanced by a generally well tolerated safety profile, it has the potential to be an efficacious disease-modifying therapy for FOP.

Die Behandlung von **Hepatitis C** hat sich in den letzten Jahren grundlegend revolutioniert. Heute ist die Erkrankung durch moderne Medikamente in fast allen Fällen schnell, unkompliziert und nahezu nebenwirkungsfrei heilbar.

Hier ist eine Übersicht über den aktuellen Therapiestandard:

### 1. Die Medikamente: Direkt wirkende Antiviralia (DAA)

Die veraltete, langwierige und extrem nebenwirkungsreiche Therapie mit Interferon-Spritzen wird heute **nicht mehr angewendet**. Stattdessen kommen hochwirksame Tabletten zum Einsatz, die sogenannten **Direct-Acting Antivirals (DAA)**.

- **Wirkweise:** Sie greifen gezielt in den Vermehrungszyklus des Hepatitis-C-Virus (HCV) ein und blockieren diesen vollständig. In der Regel werden Kombinationen aus verschiedenen Wirkstoffklassen eingesetzt, um Resistenzen zu verhindern.
- **Pangänotypische Therapien:** Früher musste vorab der genaue Genotyp des Virus (Typ 1 bis 6) bestimmt werden. Heute gibt es Medikamente, die gegen **alle Genotypen gleichermaßen wirken** (z. B. *Sofosbuvir* / *Velpatasvir* oder *Glecaprevir* / *Pibrentasvir*)

## Hepatitis C auf einen Blick

Hepatitis C (HCV) ist eine **Virusinfektion der Leber**.

-  Die **Übertragung** erfolgt vor allem über **Blut**, zum Beispiel beim gemeinsamen Gebrauch von Spritzen oder anderem Injektionszubehör.
-  Die **Infektion verläuft häufig ohne Beschwerden** und bleibt deshalb oft lange unentdeckt.
-  Eine **Schutzimpfung** gibt es bisher nicht.

 Mit direkt antiviral wirksamen Medikamenten können mehr als 95 % der chronischen Hepatitis-C-Infektionen geheilt werden.

Robert Koch-Institut 



# 8 weeks versus 12 weeks of sofosbuvir–velpatasvir for treatment-naïve, non-cirrhotic, chronic hepatitis C (RESOLVE): a multicentre, open-label, non-inferiority, randomised controlled trial in India

## Summary

**Background** Chronic hepatitis C virus (HCV) infection without cirrhosis can be treated with 12 weeks of sofosbuvir–velpatasvir combination therapy. We aimed to assess whether a shorter 8-week treatment regimen of this combination was non-inferior to the standard 12-week regimen in successfully clearing HCV infection in HCV-infected patients without evidence of cirrhosis.

**Methods** RESOLVE was a multicentre, open-label, non-inferiority, randomised controlled trial, conducted in five publicly funded hospitals in India. We randomly assigned (1:1) treatment-naïve adults (aged  $\geq 18$  years) with non-cirrhotic HCV mono-infection to receive sofosbuvir 400 mg and velpatasvir 100 mg (orally, daily) for either 8 weeks or 12 weeks. The primary outcome was the proportion of participants with sustained virological response—ie, absence of quantifiable HCV RNA at 12 weeks after treatment completion (SVR12), with 95% assumed proportion with 12-week treatment, 5% non-inferiority margin, 2.5% one-sided alpha error, and 90% study power in the per-protocol population. The trial was registered with the Clinical Trial Registry of India, CTRI/2022/03/041368, and is complete.

**Findings** Between May 15, 2022, and Sept 10, 2024, we screened 1620 participants, of whom 880 (54.3%) were enrolled in the study and randomly assigned to the 12-week (n=437 [50%]) or 8-week (n=443 [50%]) groups. 455 (52%) participants were women, 425 (48%) were men, and the median age was 35 years (IQR 28 to 47). 816 (93%) participants completed the intended 12-week (401 [92%] of 437) or 8-week (415 [94%] of 443) treatment and SVR12 testing. On per-protocol analysis, the proportion reaching SVR12 with 8-week treatment (410/415; 98.8% [95% CI 97.2 to 99.6]) was non-inferior to 12-week treatment (397/401; 99.0% [97.5 to 99.7]), with a risk difference of 0.2% (–1.5 to 1.9). Further, on intention-to-treat analysis, the proportion of participants reaching SVR12 with 8-week treatment (414/443; 93.5% [90.9 to 95.5]) was non-inferior to 12-week treatment (401/437; 91.8% [88.8 to 94.2]) with a risk difference of –1.7% (–5.2 to 1.9). No participant had any drug-related serious adverse event or drug discontinuation due to an adverse event.

**Interpretation** An 8-week regimen of sofosbuvir–velpatasvir was similar in efficacy to the standard 12-week treatment in individuals with chronic HCV infection without cirrhosis. This finding supports shortening the duration of treatment in such patients.

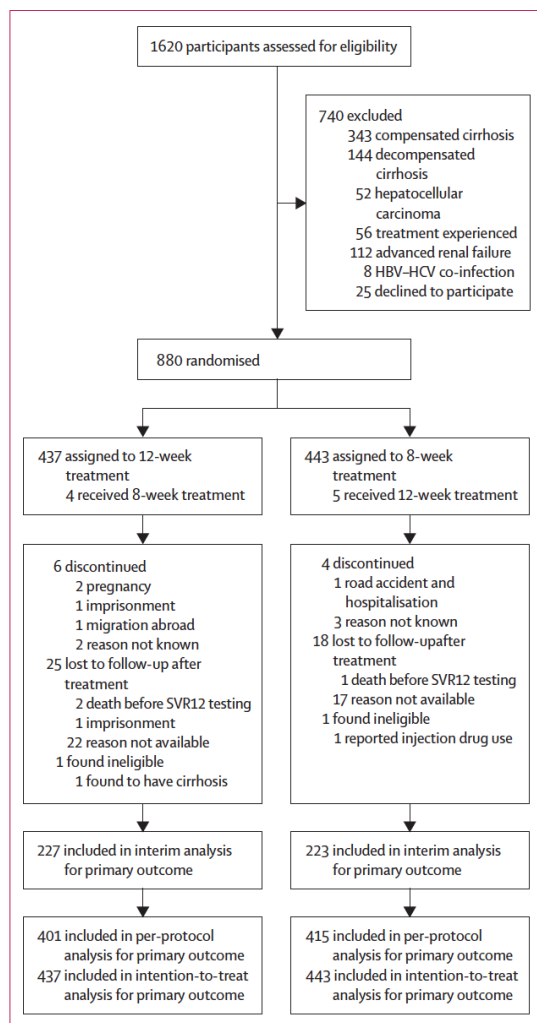


**Figure 1: Trial profile**  
HBV=hepatitis B virus. HCV=hepatitis C virus. SVR12=sustained virological response at 12 weeks after stopping treatment.

|                                                  | Per-protocol analysis |                       |                      | Intention-to-treat analysis |                       |                      |
|--------------------------------------------------|-----------------------|-----------------------|----------------------|-----------------------------|-----------------------|----------------------|
|                                                  | Total (n=816)         | 12-week group (n=401) | 8-week group (n=415) | Total (n=880)               | 12-week group (n=437) | 8-week group (n=443) |
| Number of study sites                            | 5                     | 5                     | 5                    | 5                           | 5                     | 5                    |
| Age, years                                       | 35 (28–47)            | 36 (28–48)            | 34 (28–46)           | 35 (28–47)                  | 36 (28–48)            | 34 (28–47)           |
| Sex                                              |                       |                       |                      |                             |                       |                      |
| Female                                           | 427 (52%)             | 213 (53%)             | 214 (52%)            | 455 (52%)                   | 227 (52%)             | 228 (51%)            |
| Male                                             | 389 (48%)             | 188 (47%)             | 201 (48%)            | 425 (48%)                   | 210 (48%)             | 215 (49%)            |
| BMI, kg/m <sup>2</sup>                           | 22.2 (19.6–24.7)      | 22.1 (19.5–24.6)      | 22.5 (19.6–24.8)     | 22.2 (19.6–24.8)            | 22.1 (19.5–24.7)      | 22.5 (19.6–24.9)     |
| Associated condition                             |                       |                       |                      |                             |                       |                      |
| Diabetes                                         | 36 (4%)               | 17 (4%)               | 19 (5%)              | 38 (4%)                     | 17 (4%)               | 21 (5%)              |
| Hypertension                                     | 29 (4%)               | 14 (4%)               | 15 (4%)              | 29 (3%)                     | 14 (3%)               | 15 (3%)              |
| Haemoglobin, g/dL                                | 13.0 (11.6–14.5)      | 13.0 (11.7–14.6)      | 12.9 (11.5–14.5)     | 13.0 (11.6–14.6)            | 13.0 (11.7–14.6)      | 13.0 (11.5–14.5)     |
| White cell count, × 10 <sup>3</sup> per µL       | 7.2 (5.6–8.7)         | 7.0 (5.6–8.7)         | 7.4 (5.8–8.7)        | 7.2 (5.6–8.8)               | 7.0 (5.6–8.8)         | 7.4 (5.8–8.7)        |
| Platelet count, × 10 <sup>3</sup> per µL         | 186 (150–238)         | 183 (150–239)         | 188 (150–238)        | 185 (148–239)               | 181 (148–239)         | 188 (148–239)        |
| Total bilirubin, mg/dL                           | 0.6 (0.5–0.9)         | 0.6 (0.4–0.8)         | 0.6 (0.5–0.9)        | 0.6 (0.5–0.9)               | 0.6 (0.5–0.8)         | 0.6 (0.5–0.9)        |
| Total serum protein, g/dL                        | 7.7 (7.3–8.1)         | 7.7 (7.3–8.1)         | 7.8 (7.3–8.1)        | 7.7 (7.3–8.1)               | 7.7 (7.3–8.1)         | 7.8 (7.3–8.2)        |
| Albumin, g/dL                                    | 4.4 (4.2–4.7)         | 4.4 (4.1–4.6)         | 4.4 (4.2–4.7)        | 4.4 (4.2–4.7)               | 4.4 (4.1–4.7)         | 4.4 (4.2–4.7)        |
| Alanine aminotransferase, IU/L                   | 63 (41–103)           | 65 (40–102)           | 62 (42–106)          | 63 (41–104)                 | 66 (41–104)           | 62 (41–106)          |
| Aspartate aminotransferase, IU/L                 | 52 (37–80)            | 53 (37–81)            | 52 (38–77)           | 53 (37–81)                  | 53 (37–82)            | 51 (37–76)           |
| Serum alkaline phosphatase, IU/L                 | 180 (114–247)         | 172 (114–236)         | 187 (116–255)        | 178 (113–247)               | 169 (111–236)         | 185 (114–254)        |
| Prothrombin time, international normalised ratio | 1.0 (1.0–1.1)         | 1.0 (1.0–1.1)         | 1.0 (1.0–1.1)        | 1.0 (1.0–1.1)               | 1.0 (1.0–1.1)         | 1.0 (1.0–1.1)        |
| Serum creatinine, mg/dL                          | 0.8 (0.7–1.0)         | 0.8 (0.7–1.0)         | 0.8 (0.7–1.0)        | 0.8 (0.7–1.0)               | 0.8 (0.7–1.0)         | 0.8 (0.7–1.0)        |
| Liver stiffness, KPa*                            | 6.2 (5.0–7.9)         | 6.3 (5.0–7.9)         | 6.2 (4.9–7.9)        | 6.2 (4.9–7.9)               | 6.3 (5.0–7.9)         | 6.1 (4.9–7.9)        |
| APRI score†                                      | 0.7 (0.5–1.2)         | 0.7 (0.5–1.2)         | 0.7 (0.5–1.1)        | 0.7 (0.5–1.2)               | 0.8 (0.5–1.2)         | 0.7 (0.5–1.1)        |
| Fibrosis-4 Index score‡                          | 1.3 (0.9–2.0)         | 1.3 (0.9–2.0)         | 1.3 (0.8–2.0)        | 1.3 (0.8–2.0)               | 1.3 (0.9–2.1)         | 1.3 (0.8–2.0)        |
| Quantitative HCV RNA, log <sub>10</sub> (IU/mL)  | 5.9 (5.1–6.6)         | 5.9 (5.0–6.6)         | 5.9 (5.2–6.7)        | 5.9 (5.2–6.6)               | 5.9 (5.1–6.6)         | 5.9 (5.2–6.7)        |
| HCV genotype‡                                    |                       |                       |                      |                             |                       |                      |
| 1                                                | 125 (16%)             | 51 (13%)              | 74 (18%)             | 130 (15%)                   | 53 (13%)              | 77 (18%)             |
| 3                                                | 661 (82%)             | 331 (85%)             | 330 (81%)            | 714 (83%)                   | 361 (85%)             | 353 (80%)            |
| 4                                                | 13 (2%)               | 7 (2%)                | 6 (1%)               | 16 (2%)                     | 9 (2%)                | 7 (2%)               |

Data are n, n (%), or median (IQR). APRI= aspartate aminotransferase-to-platelet ratio index. HCV=hepatitis C virus. \*These data were available only for a subset of participants—ie, for 369 in the 12-week group and 381 in the 8-week group for the per-protocol dataset, and for 400 in the 12-week group and 408 in the 8-week group for the intention-to-treat dataset. †These data were only available for participants in whom liver stiffness measurement was not available—ie, for 32 in the 12-week group and 34 in the 8-week group for the per-protocol dataset, and for 37 in the 12-week group and 35 in the 8-week group for the intention-to-treat dataset. ‡Data were available only for a subset of participants—ie, for 389 in the 12-week group and 410 in the 8-week group for the per-protocol dataset, and for 423 in the 12-week group and 437 in the 8-week group for the intention-to-treat dataset.

**Table 1: Baseline clinical and laboratory characteristics of participants**

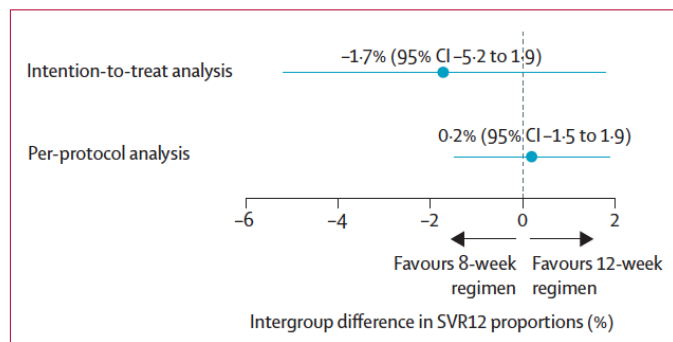


**Figure 2: Results for primary outcome showing intergroup difference in SVR12**  
 Data are shown as SVR12 in 12-week treatment minus SVR12 in 8-week treatment.  
 SVR12=sustained virological response at 12 weeks after stopping treatment.

|                                                                                                    | 12-week group              | 8-week group               | Difference in proportion with SVR12* |
|----------------------------------------------------------------------------------------------------|----------------------------|----------------------------|--------------------------------------|
| <b>Overall</b>                                                                                     |                            |                            |                                      |
| SVR12†                                                                                             |                            |                            |                                      |
| Per protocol                                                                                       | 397/401 (99.0%; 97.5–99.7) | 410/415 (98.8%; 97.2–99.6) | 0.2 (–1.5 to 1.9)                    |
| Intention to treat                                                                                 | 401/437 (91.8%; 88.8–94.2) | 414/443 (93.5%; 90.9–95.5) | –1.7 (–5.2 to 1.9)                   |
| Participants who completed their planned treatment duration and received >80% of the planned doses | 431/437 (98.6%; 97.0–99.4) | 439/443 (99.1%; 97.7–99.6) | –0.5 (–1.9 to 0.9)                   |
| <b>Genotype 3 HCV subgroup</b>                                                                     |                            |                            |                                      |
| SVR12†                                                                                             |                            |                            |                                      |
| Per protocol                                                                                       | 327/331 (98.8%; 97.6–99.9) | 328/330 (99.4%; 98.5–100)  | –0.6 (–2.5 to 1.1)                   |
| Intention to treat                                                                                 | 330/361 (91.4%; 88.5–94.3) | 332/353 (94.1%; 91.6–96.5) | –2.6 (–6.6 to 1.2)                   |

HCV=hepatitis C virus. SVR12=sustained virological response at 12 weeks after stopping treatment. \*Data for difference in proportions in the two groups (SVR12 in the 12-week group minus SVR12 in the 8-week group) are shown as observed difference (95% CI), with positive values implying that the SVR12 rate in the 12-week group was better. †Data for SVR12 are shown as actual numbers attaining SVR12/denominator (%; 95% CI).

**Table 2: Proportion of participants with SVR12 and proportions completing the planned treatment**

|                                            | Per-protocol analysis    |                         | Intention-to-treat analysis |                         |
|--------------------------------------------|--------------------------|-------------------------|-----------------------------|-------------------------|
|                                            | 12-week group<br>(n=401) | 8-week group<br>(n=415) | 12-week group<br>(n=437)    | 8-week group<br>(n=443) |
| Number attaining SVR12                     | 397 (99%)                | 410 (99%)               | 401 (92%)                   | 414 (93%)               |
| Number not attaining SVR12                 | 4                        | 5                       | 36 (8%)                     | 29 (7%)                 |
| Virological failure                        | 4                        | 5                       | 4 (1%)                      | 5 (1%)                  |
| Failure for other reasons                  |                          |                         | 32 (7%)                     | 24 (5%)                 |
| Withdrawal of consent                      | NA                       | NA                      | 0                           | 0                       |
| Protocol violation leading to exclusion    | NA                       | NA                      | 1 (<1%)                     | 1 (<1%)                 |
| Received regimen other than that allocated | NA                       | NA                      | 2 (<1%)*                    | 3 (1%)†                 |
| Premature treatment discontinuation        | NA                       | NA                      | 4 (1%)‡                     | 2 (<1%)§                |
| Loss to follow-up or missing SVR12 data    | NA                       | NA                      | 25 (6%)                     | 18 (4%)                 |

Data are n (%). NA=not applicable. SVR12=sustained virological response at 12 weeks after stopping treatment. \*Of the four participants who erroneously received the 8-week regimen (instead of the 12-week regimen), two had SVR12 and two were lost to follow-up. †Of the five participants who erroneously received the 12-week regimen (instead of the 8-week regimen), two had SVR12 and three were lost to follow-up. ‡Of the six participants in this group who discontinued treatment at 4 weeks, two had SVR12 and four were lost to follow-up. §Of the four participants in this group who discontinued treatment at 4 weeks, two had SVR12 and two were lost to follow-up.

**Table 3: Participants without SVR12 in the two treatment groups, with reasons**

|                                                                                                             | 12-week group | 8-week group |
|-------------------------------------------------------------------------------------------------------------|---------------|--------------|
| Participants                                                                                                | 437           | 443          |
| Deaths during treatment or within the 12-week follow-up period after completion of the assigned treatment * |               |              |
| Deaths during drug treatment                                                                                | 0             | 0            |
| Deaths during 0–4 weeks post-treatment                                                                      | 1*            | 0            |
| Deaths during 4–12 weeks post-treatment                                                                     | 1†            | 1†           |
| Other serious adverse events assessed as related to study drugs                                             | 0             | 0            |
| Adverse events leading to discontinuation of treatment                                                      | 0             | 0            |

Data are n. SVR12=sustained virological response at 12 weeks after stopping treatment. \*This person died at 2 weeks after completion of drug treatment due to suspected myocardial infarction. †The death in the 12-week group was related to a road-traffic accident, and the death in the 8-week group was due to probable myocardial infarction.

**Table 4: Participants with serious adverse events and without SVR12 in the two treatment arms, with reasons**

### Implications of all the available evidence

Our findings expand upon previous observational data and confirm that a shorter 8-week regimen of sofosbuvir–velpatasvir has efficacy similar to that of the 12-week regimen of this combination in treating HCV infection in patients without evidence of cirrhosis. This shorter regimen is expected to offer substantial cost savings and logistical advantages, and might help improve treatment uptake and completion rates. Hence, public health programmes aimed at the elimination of hepatitis C should consider using this shorter treatment regimen.



# The *Lancet* Commission on 21st century global threats to health

(A 59-page report)

## Executive Summary

This report from the *Lancet* Commission on 21st century global threats to health lays out a foresight-driven, health-focused approach to identifying and prioritising major threats to global health over the remainder of the century. We argue that recent global shocks (including COVID-19, Ebola Bundibugyo virus disease, major geopolitical conflict, accelerating climate impacts, rapid shifts in development assistance, and the emergence of powerful artificial intelligence [AI] systems) show how quickly assumptions about stability can be overturned—and why governments and multilateral institutions must counter short-termism and localism with systematic, repeatable risk assessment and preparedness planning.

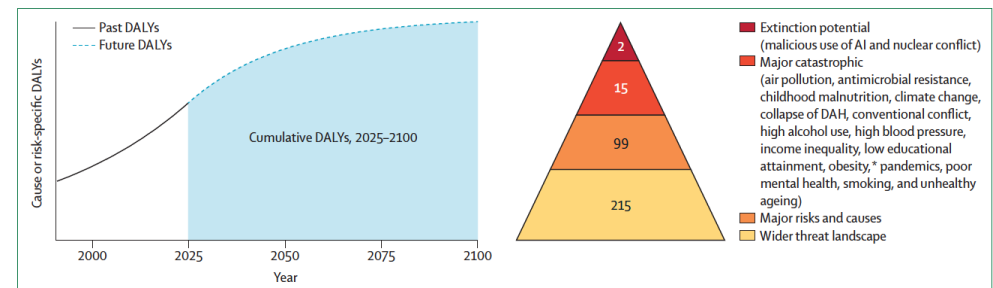


Figure 1: Pyramid of threats

The pyramid shows diseases, injuries, risks, socioeconomic factors, and other threats classified by severity of harm (ie, cumulative attributable DALYs). The graph schematic shows cumulative DALY calculation per health entity estimated using the reference scenario. The dashed reference scenario forecasts each cause or risk forward to 2100; the shaded area is the cumulative burden (DALYs) accumulated between 2025 and 2100. Major catastrophic and extinction potential threats met the Commission criteria accounting for more than 1 billion cumulative DALYs to the end of the century. AI=artificial intelligence. DAH=development assistance for health. DALYs=disability-adjusted life-years. \* Obesity refers to the cluster of high BMI, poor diet, and low physical activity risks.

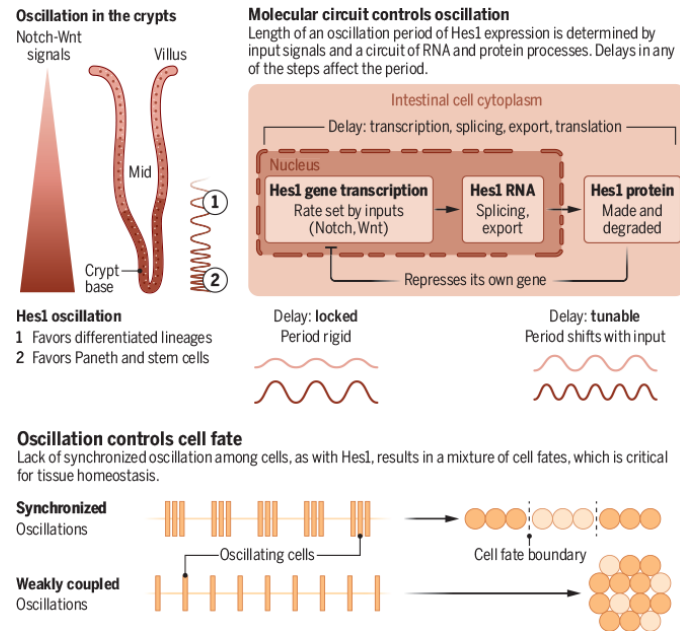
Ein **DALY** (engl. *Disability-Adjusted Life Year*, auf Deutsch: *behinderungsbereinigtes Lebensjahr*) ist ein Maß für die Gesamtkrankheitslast einer Bevölkerung. 1 DALY entspricht dem Verlust eines vollkommen gesunden Lebensjahres





## Keeping time in the crypt

To maintain homeostasis, barrier epithelia—the body’s first line of defense—undergo constant, rapid turnover. This includes the inner surface of the mammalian intestine, where ongoing regeneration protects against daily wear and tear, preventing dangerous breaches and supporting gut health. The correct proportion of cell types is maintained throughout lifetimes, ensuring that form and function are preserved. Although the signaling pathways required for this balance are known, it has been unclear how their inputs are tuned to appropriately apportion cell fates. Weterings *et al.* report that cell type specification is encoded by the frequency of oscillations in expression of the transcription factor Hes1 (hairy and enhancer of split 1). They found that distinct oscillation time periods tracked with specific cell identities and that oscillating signaling dynamics, known to play a role in developmental processes, appear to control homeostatic processes as well.



## Specification by oscillation

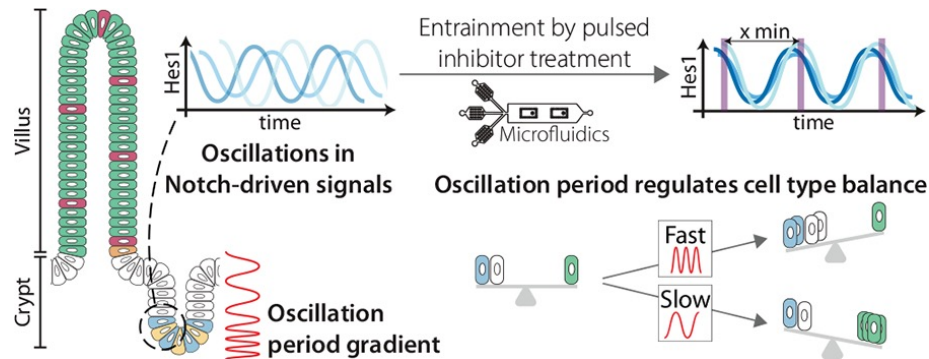
Epithelial cells lining the mammalian intestine arise from the differentiation of stem cells. This involves Notch and Wnt signaling coupled to oscillations in the expression of Hes1. Oscillation frequencies promote distinct cell fates.

# Frequency encoding regulates cell type composition in the small intestine

**INTRODUCTION:** The intestinal epithelium constantly renews itself, requiring precise balance between stem cell self-renewal and differentiation into absorptive and secretory cell types. The Notch signaling pathway is known to regulate this process: High Notch activity promotes absorptive cell fates, whereas low activity drives secretory differentiation. But how the gut achieves and maintains a balanced ratio of cell types has remained unclear. One candidate regulator is Hes 1 (hairy and enhancer of split 1), a Notch target protein that has an intrinsic propensity to oscillate owing to its own repressive feedback loop. Whether such oscillatory behavior plays a functional role in intestinal cell fate decisions had not previously been tested.

**RATIONALE:** We hypothesized that biological information for cell fate specification could be encoded in the dynamics—rather than merely the level—of Notch-driven oscillations, a concept known as dynamic signal encoding. To test this, we used a fluorescent Hes1 reporter mouse line to visualize Hes1 dynamics in living intestinal tissue and organoids at single-cell resolution. We combined high-throughput live imaging, automated single-cell tracking, time series analysis, and a custom microfluidic system that delivers periodic pulses of a Notch-signaling inhibitor to experimentally modulate the dynamics of Hes1 oscillations in organoids.

**RESULTS:** Hes1 oscillates with ultradian periodicity (roughly 75 to 200 min) in intestinal stem and progenitor cells both in vivo and in organoids. Quantitative single-cell tracking revealed a spatial gradient of oscillation frequency: Cells near the crypt base oscillate rapidly (~90-min period), whereas cells further along the crypt-villus axis oscillate progressively more slowly (~170-min period). Both Notch and Wnt (wingless-related integration site) signaling, as well as cell cycle phase, modulate this gradient. Using our microfluidic entrainment system, we showed that imposing 90-min oscillations increases stem and progenitor cells as well as Paneth cell numbers, whereas 130-min oscillations promote the broader secretory lineage. Notably, these effects were not caused by changes in overall Notch signal levels, confirming that oscillation frequency itself carries instructive information.



**Frequency encoding of intestinal cell fate.** Notch-driven Hes1 oscillations occur throughout the intestinal crypt and form a period gradient from the crypt base toward the villus. Their dynamics are modulated by cell cycle progression as well as Wnt and Notch signaling. Experimental entrainment of endogenous oscillations demonstrates that specific oscillation frequencies promote distinct cell fates, revealing frequency as an additional layer of information encoding that contributes to intestinal cell fate specification.

**CONCLUSION:** We provide evidence that frequency encoding—the transmission of biological information through the periodicity of a molecular oscillation—regulates cell type composition in the intestinal epithelium. Specific Hes1 oscillation frequencies promote distinct cell fates: Fast oscillations favor stem cell maintenance and Paneth cell differentiation, whereas slower oscillations are associated with other secretory cell differentiation. The Hes1 oscillatory network appears to serve as an integration hub for multiple upstream signals, translating them into differentiation outcomes through frequency modulation. This mechanism may have broader implications for understanding tissue homeostasis, regeneration, and cancer.



# The surprising way walking can benefit your brain



What do Albert Einstein, Virginia Woolf, Stephen King, Henry David Thoreau and Friedrich Nietzsche have in common?

They all credit walking as essential for helping their creative thinking.

Though walking may seem mundane, it has many health benefits, including improving longevity and making your brain younger. Research also shows that walking helps people come up with an essential ingredient for creativity.

“It really helps you generate ideas, novel ideas, original ideas,” said Alex Thabane, a researcher at McMaster University and the lead author of a recent meta-analysis that looked at walking and creativity.

## Walking inspires new ideas

By definition, creativity is a cognitive ability that lets you generate something new and useful. To be creative, you need to use two types of thinking: divergent and convergent.

Divergent thinking is a spontaneous process that generates many different new ideas. Convergent thinking evaluates the quality of these ideas and narrows them down to find the best option.



# The impact of walking on creative thinking: A systematic review and meta-analysis



## Abstract

### Background

Walking is associated with many benefits, from improved mental health to a reduced risk of mortality – but can it boost creative thinking? Current evidence suggests a positive effect of physical activity on creative thinking, but the specific effect of walking has not been adequately explored.

### Methods

We conducted a systematic search of the PsycINFO, MEDLINE, Scopus, and ProQuest databases from inception to 8 January 2025 using search terms related to walking and creativity. We then performed meta-analyses of Cohen's  $d$  effect sizes to assess the effect of walking on creative thinking, as represented by divergent thinking (the ability to generate novel and useful ideas) and convergent thinking (the ability to analyze and select ideas to find the best solution). We assessed study quality using a creativity-specific tool, and the certainty of the evidence with the Grading of Recommendations Assessment, Development and Evaluation Framework.

### Results

We identified 23 studies (12 randomized experimental studies, nine non-randomized experimental studies, two observational studies) from 16 articles including a total of 1,036 participants, most of whom were post-secondary students. We found moderate certainty evidence of a large effect of walking on divergent thinking ( $d=0.93$  [95% CI 0.44, 1.42]), and very uncertain evidence of a null effect of walking on convergent thinking ( $d=0.16$  [95% CI  $-0.31$ , 0.63]). Sensitivity analyses of randomized trials only found similarly large effects of walking on divergent thinking ability ( $d=0.82$  [95% CI 0.35, 1.28]).

### Conclusion

Results suggest that walking likely results in a large increase in divergent thinking, indicating its potential as an intervention to stimulate creative idea generation.