

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

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

Usually every Wednesday 17:00 - 18:00



Klinische Forschung

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

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



The radiograph showed dense, transverse bands of metaphyseal sclerosis in the radius, ulna, metacarpals and phalanges. In the context of acute encephalopathy and seizures, these findings were suspected to represent “lead lines” as seen in severe lead poisoning. While radiographs are not recommended in the diagnostic workup of lead poisoning, the presence of lead lines may help make a delayed diagnosis. The blood lead level was elevated, confirming the diagnosis.

A 6-month-old baby boy was transferred to a quaternary children’s hospital for evaluation and management of seizures. One week earlier, he had had decreased oral intake, vomiting, and irritability. Laboratory testing showed hypocalcemia, hypophosphatemia, and microcytic anemia. Radiography of the left hand and wrist to evaluate hypocalcemia is shown. What is the most likely diagnosis?

Congenital syphilis

Hypoparathyroidism

☒ Lead poisoning

Osteopetrosis

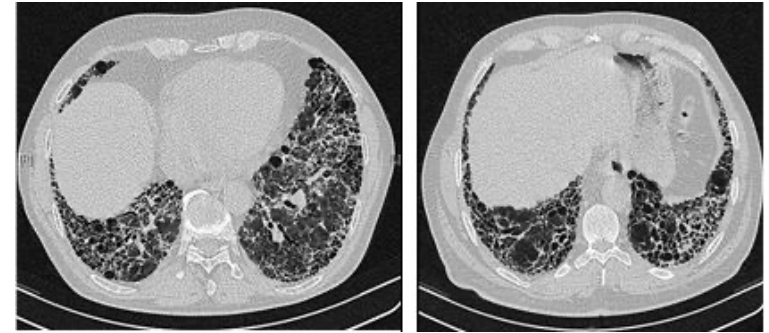
Rickets

Die **idiopathische pulmonale Fibrose (IPF)** ist eine fortschreitende, unheilbare Vernarbung des Lungengewebes unbekannter Ursache. Sie betrifft meist Menschen ab 50 Jahren und führt zu zunehmender Atemnot und trockenem Husten. Der Verlauf und die Prognose sind oft schwerwiegend, doch Behandlungen können das Fortschreiten verlangsamen.

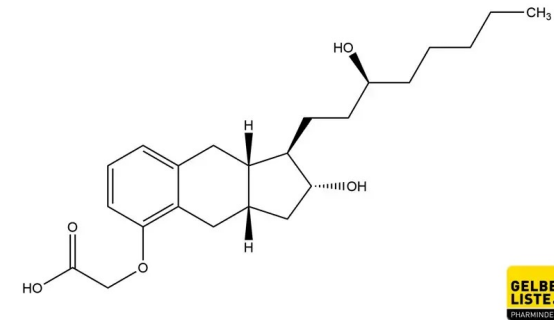
Symptome

Die Krankheit beginnt oft schleichend. Typische Anzeichen sind:

- **Atemnot:** Zunächst nur bei körperlicher Belastung, später auch in Ruhe.
- **Reizhusten:** Ein trockener, hartnäckiger Husten ohne Auswurf.
- **Leistungsminderung:** Abgeschlagenheit und allgemeine Schwäche.
- **Spätstadien:** Häufig kommt es zu Uhrglasnägeln oder Trommelschlegelfingern (Veränderungen an den Fingerenden) sowie Blaufärbung der Lippen (Zyanose).



Treprostinil ist ein künstlich hergestellter Arzneistoff aus der Gruppe der **Prostacyclin-Analoga**, der primär zur Behandlung von schwerem **Lungenhochdruck** (pulmonaler arterieller Hypertonie, PAH) eingesetzt wird. Er erweitert die Blutgefäße in der Lunge, senkt dort den Blutdruck und verbessert so die körperliche Leistungsfähigkeit der Patienten.

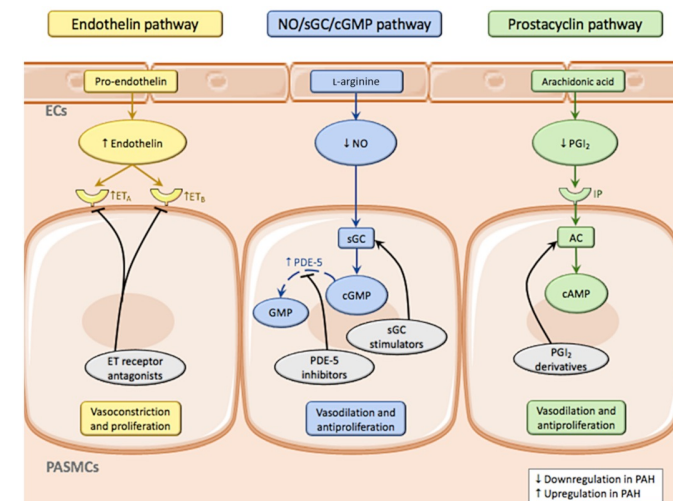


Treprostinil is a synthetic analog of prostacyclin, which is also known as prostaglandin I₂ (PGI₂)

Gefäßerweiterung: Er entspannt die glatte Muskulatur der Lungenarterien.

Thrombozytenhemmung: Er verhindert, dass Blutplättchen verklumpen.

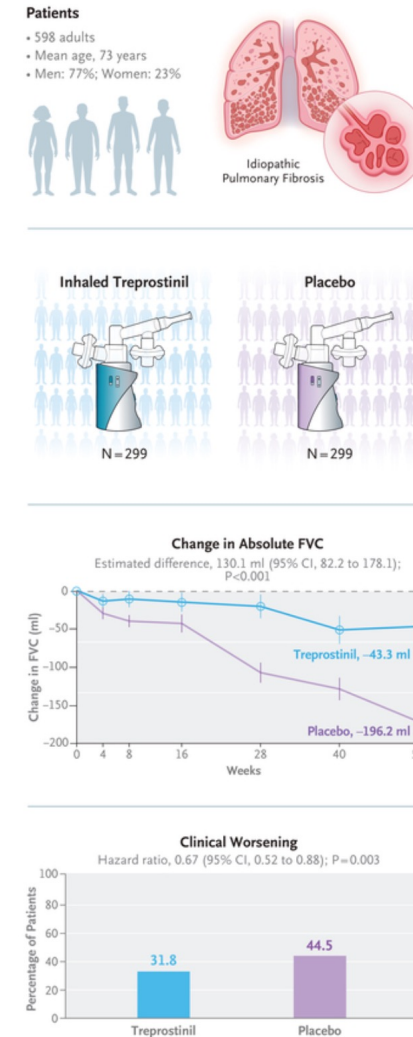
Zellhemmung: Er wirkt dem krankhaften Wachstum von Zellen in den Gefäßwänden entgegen.



Phase 3 Trials of Inhaled Treprostinil for Idiopathic Pulmonary Fibrosis

Two phase 3, randomized trials of inhaled treprostinil for idiopathic pulmonary fibrosis (IPF) were conducted on the basis of preclinical and clinical evidence of an antifibrotic mechanism. TETON-2 was completed first, and results were published; the results of TETON-1 and of both trials combined are reported here.

In the double-blind TETON-1 trial, we randomly assigned patients with IPF to receive inhaled treprostinil or placebo (12 breaths four times daily). The primary end point was the change in forced vital capacity (FVC) at week 52. Secondary end points, which were analyzed in a prespecified order to control for multiplicity, were clinical worsening (the first occurrence of death from any cause, hospitalization for a respiratory cause, or a relative decline of $\geq 10\%$ in the percentage of predicted FVC) and acute exacerbation of IPF (each assessed in a time-to-event analysis), survival, change in percentage of predicted FVC, quality of life, and change in diffusion capacity of the lungs for carbon monoxide at week 52.



Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disorder for which there are now three approved therapies. However, the prognosis remains poor, and there is an ongoing need for further effective therapies.

Inhaled treprostinil has been shown to have multimodal activity across fibrotic, vascular, and inflammatory pathways, which set the foundation for the current trial. The 16-week INCREASE trial involving patients with interstitial lung disease and associated pulmonary hypertension provided evidence that inhaled treprostinil may have a significant benefit over placebo in preserving forced vital capacity (FVC). These results, together with further suggestive evidence from an open-label extension trial, provided a rationale for studying inhaled treprostinil in patients with IPF.

Patients

Eligible patients were 40 years of age or older, had a diagnosis of IPF that was based on the 2018 clinical practice guidelines of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society, and had an FVC that was at least 45% of the predicted value. High-resolution computed tomographic scans were reviewed centrally, as were surgical lung-biopsy specimens (when available).

Trial Procedures

Patients were randomly assigned in a 1:1 ratio to receive inhaled treprostinil or placebo. Randomization was stratified according to IPF background therapy (nintedanib or pirfenidone vs. no background therapy). All the patients began receiving inhaled treprostinil or placebo at a dose of 3 breaths (18 µg) administered four times daily, and the dose was adjusted to reach a target of 12 breaths (72 µg) four times daily or the maximum clinically tolerated dose. Treprostinil inhalation solution or placebo was administered with the TD-300 ultrasonic nebulizer.

End Points

The primary end point of the trial was the change from baseline in absolute FVC at week 52. Spirometry results were reviewed centrally.

Secondary efficacy end points included clinical worsening (a composite of death from any cause, hospitalization for an adjudicated respiratory cause, or a relative decline of at least 10% in the percentage of predicted FVC) and an acute exacerbation of IPF, each of which was assessed in a time-to-event analysis.

Characteristic	Treprostinil (N = 299)	Placebo (N = 299)	All Patients (N = 598)
Female sex — no. (%)	71 (23.7)	65 (21.7)	136 (22.7)
Age			
Mean (range) — yr	72.6 (52–91)	73.3 (53–89)	73.0 (52–91)
Distribution — no. (%)			
<65 yr	32 (10.7)	29 (9.7)	61 (10.2)
65 to <80 yr	222 (74.2)	218 (72.9)	440 (73.6)
≥80 yr	45 (15.1)	52 (17.4)	97 (16.2)
Race or ethnic group — no. (%) [†]			
White	270 (90.3)	271 (90.6)	541 (90.5)
Black or African American	5 (1.7)	6 (2.0)	11 (1.8)
American Indian or Alaska Native	2 (0.7)	1 (0.3)	3 (0.5)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	1 (0.2)
Asian	14 (4.7)	11 (3.7)	25 (4.2)
Multiple	1 (0.3)	4 (1.3)	5 (0.8)
Unknown	7 (2.3)	5 (1.7)	12 (2.0)
Hispanic or Latino ethnic group — no. (%) [†]			
Yes	13 (4.3)	17 (5.7)	30 (5.0)
No	279 (93.3)	276 (92.3)	555 (92.8)
Not reported	4 (1.3)	4 (1.3)	8 (1.3)
Unknown	3 (1.0)	2 (0.7)	5 (0.8)
Time since diagnosis of IPF — yr	3.54±3.02	3.62±3.05	3.58±3.03
Smoking status — no. (%)			
Never	125 (41.8)	119 (39.8)	244 (40.8)
Current	3 (1.0)	4 (1.3)	7 (1.2)
Former	171 (57.2)	176 (58.9)	347 (58.0)
Use of supplemental oxygen — no. (%)	54 (18.1)	63 (21.1)	117 (19.6)
FVC			
Mean — ml	2699.5±753.5	2747.1±780.7	2723.3±767.0
% of predicted value	73.9±16.3	75.4±18.1	74.6±17.3
Median NT-proBNP (IQR) — pg/ml	95.5 (46.0–205.0)	89.0 (48.0–214.0)	91.0 (48.0–206.0)
DLco — % of predicted value	48.3±16.0	49.8±20.4	49.0±18.3
Background therapy — no. (%)			
None	68 (22.7)	66 (22.1)	134 (22.4)
Nintedanib	132 (44.1)	143 (47.8)	275 (46.0)
Pirfenidone	99 (33.1)	90 (30.1)	189 (31.6)

Adverse Events.

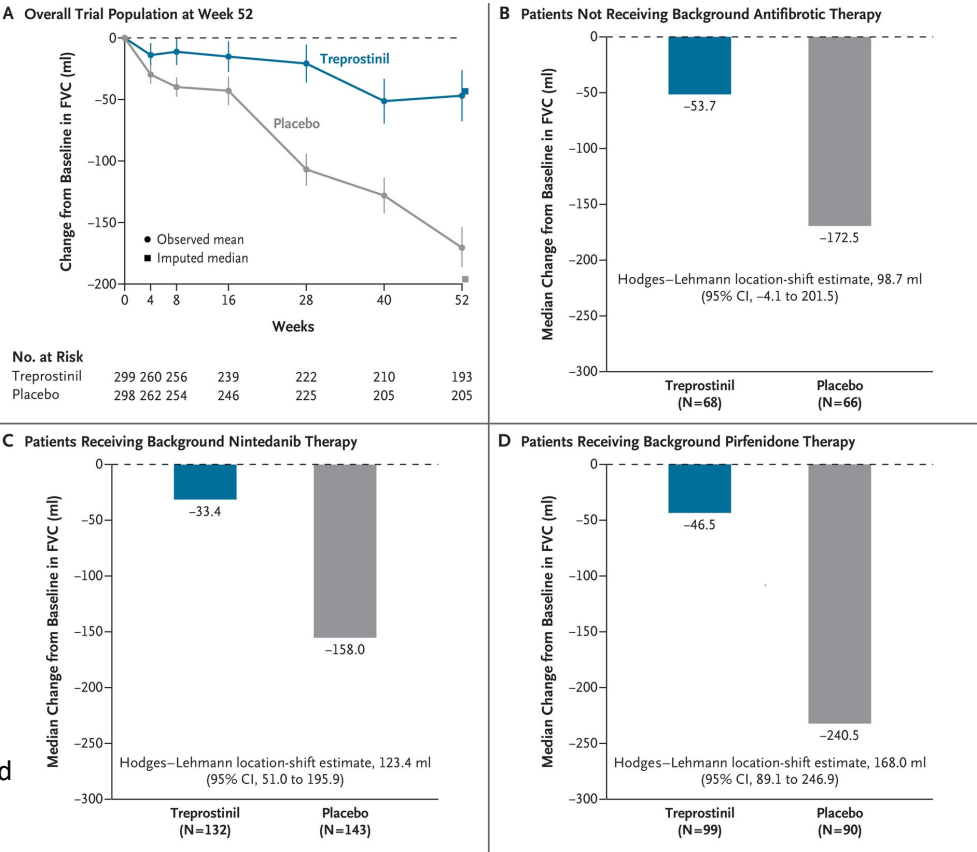
End Point	Treprostinil (N = 299)	Placebo (N = 299)	Hodges–Lehmann Estimate (95% CI) [*]	Hazard Ratio (95% CI) [†]
Primary end point				
Median change in absolute FVC from baseline to week 52 (95% CI) — ml‡	–43.3 (–92.1 to –9.1)	–196.2 (–227.1 to –155.6)	130.1 (82.2 to 178.1)§	
Secondary end points				
Clinical worsening — no. of patients (%)¶				
Any clinical-worsening event	95 (31.8)	133 (44.5)		0.67 (0.52 to 0.88)‖
Death from any cause	5 (1.7)	9 (3.0)		
Hospitalization for an adjudicated respiratory cause	22 (7.4)	33 (11.0)		
Relative decline of ≥10% in % of predicted FVC	68 (22.7)	91 (30.4)		
Acute exacerbation of IPF — no. of patients (%)**	10 (3.3)	19 (6.4)		0.50 (0.23 to 1.08)
Death by week 52 — no. of patients (%)	22 (7.4)	32 (10.7)		0.65 (0.38 to 1.13)
Median change in % of predicted FVC, baseline to week 52 (95% CI) — percentage points‡††	–1.4 (–2.5 to –0.3)	–5.4 (–6.2 to –4.7)	3.7 (2.4 to 5.0)	
Median change in K-BILD total score, baseline to week 52 (95% CI) — points‡††‡‡	–1.1 (–2.1 to 0.0)	–2.4 (–3.8 to –1.2)	1.4 (–0.2 to 2.9)	
Median change in % of predicted DLco, baseline to week 52 (95% CI) — percentage points‡††	–3.3 (–4.8 to –1.5)	–4.0 (–5.6 to –3.0)	1.9 (–0.2 to 3.9)	

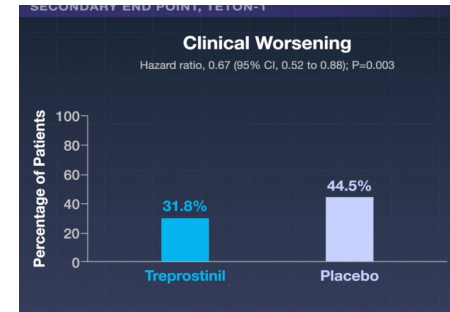
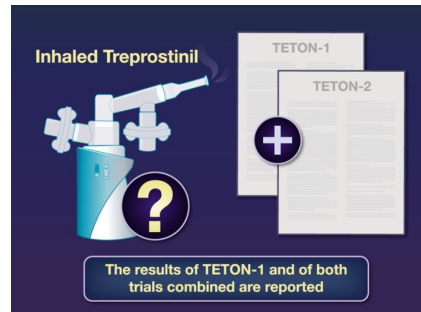
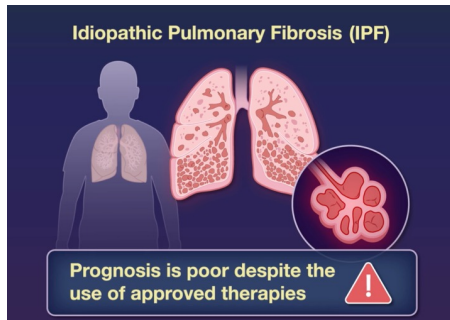
Primary and Secondary End Points for Combined TETON-1 and TETON-2 Trials.

End Point	Treprostinil (N = 597)	Placebo (N = 594)	Hodges–Lehmann Estimate (95% CI) ^a	Hazard Ratio (95% CI) [†]
Primary end point				
Median change in absolute FVC from baseline to week 52 (95% CI) — ml‡	-45.4 (-73.8 to -23.1)	-161.7 (-194.5 to -134.1)	111.8 (79.7 to 144.0)	
Secondary end points				
Clinical worsening — no. of patients (%)§				
Any clinical-worsening event	176 (29.5)	248 (41.8)		0.69 (0.57 to 0.84)
Death from any cause	9 (1.5)	12 (2.0)		
Hospitalization for an adjudicated respiratory cause	52 (8.7)	71 (12.0)		
Relative decline of ≥10% in % of predicted FVC	115 (19.3)	165 (27.8)		
Acute exacerbation of IPF — no. of patients (%)¶	19 (3.2)	36 (6.1)		0.52 (0.30 to 0.91)
Death by week 52 — no. of patients (%)	41 (6.9)	56 (9.4)		0.71 (0.47 to 1.06)
Median change in % of predicted FVC, baseline to week 52 (95% CI) — percentage points‡	-1.4 (-2.0 to -0.7)	-4.7 (-5.4 to -3.9)	3.2 (2.3 to 4.1)	
Median change in K-BILD total score, baseline to week 52 (95% CI) — points‡ **	-1.0 (-1.7 to -0.1)	-2.6 (-3.4 to -1.5)	1.9 (0.7 to 3.0)	
Median change in % of predicted DLco, baseline to week 52 (95% CI) — percentage points‡	-3.0 (-4.0 to -2.2)	-4.0 (-5.1 to -3.4)	1.9 (0.5 to 3.4)	

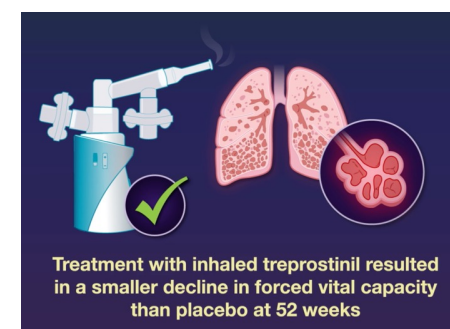
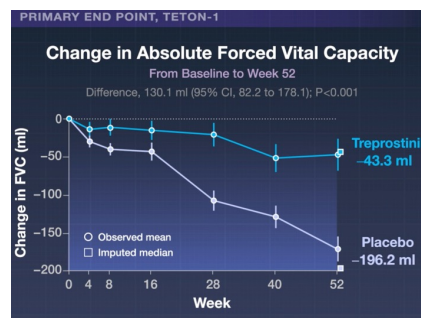
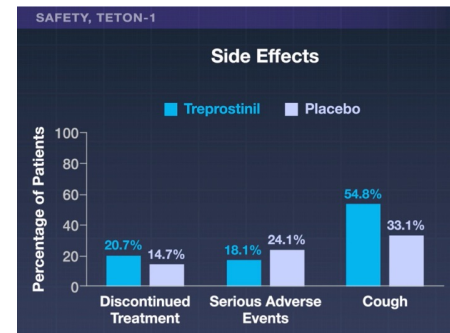
Change over Time in Absolute Forced Vital Capacity (FVC) in TETON-1.

Panel A shows the changes from baseline in the absolute FVC over the 52-week trial period. The data shown are the observed mean changes that were calculated with the values obtained at the trial visits, as well as the median changes that included imputed values at week 52. Panels B, C, and D show the change from baseline in the absolute FVC at week 52 according to the use of background therapy. The data shown are the median changes that included imputed values at week 52. The 95% confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.





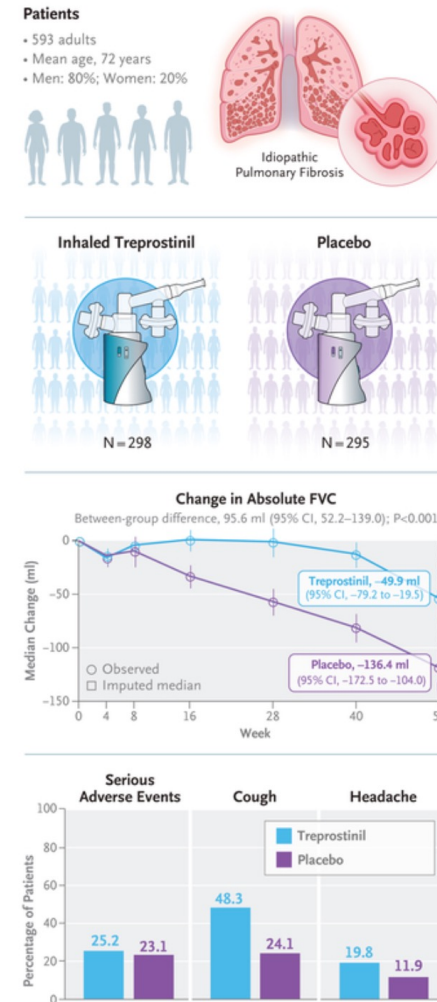
Unfortunately, both got worse.



Inhaled Treprostinil for Idiopathic Pulmonary Fibrosis

Preclinical data indicate that inhaled treprostinil may be useful for the treatment of idiopathic pulmonary fibrosis (IPF) through an antifibrotic mechanism, a premise that is supported by clinical observation.

In this phase 3, double-blind trial, we randomly assigned patients with IPF to receive inhaled treprostinil or placebo (12 breaths four times daily) over a period of 52 weeks. The primary end point was the change from baseline in the absolute forced vital capacity (FVC) at week 52. Secondary end points, which were analyzed in a prespecified order to control for multiplicity, were clinical worsening and acute exacerbation of IPF (each assessed in a time-to-event analysis), death by week 52, and the change from baseline in the percentage of predicted FVC, quality of life, and the diffusing capacity of the lungs for carbon monoxide by week 52. Safety was also assessed.



Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disorder that is associated with a poor prognosis, with a median survival of 3 to 5 years if the disease is untreated. The cause remains uncertain, but genetic predisposition, aging, and environmental exposures all probably have a role. The course of the disease tends to be progressive and unpredictable, and death occurs as a result of progressive respiratory failure. The antifibrotic agents nintedanib and pirfenidone were approved for the treatment of IPF in 2014, and since completion of the present trial, nerandomilast has also been approved.

Inhaled treprostinil has previously been shown to improve exercise capacity in patients with group 1 pulmonary hypertension (pulmonary arterial hypertension) and in those with group 3 pulmonary hypertension (pulmonary hypertension associated with interstitial lung disease). A post hoc analysis of the INCREASE trial involving patients with pulmonary hypertension associated with interstitial lung disease suggested that inhaled treprostinil showed a significant benefit over placebo with respect to forced vital capacity (FVC) at 16 weeks. In addition, patients who had previously received placebo in the INCREASE trial had increases in FVC when they transitioned to inhaled treprostinil in the open-label extension study. These clinical results laid the foundation for the hypothesis that inhaled treprostinil could prevent decline in lung function in patients with fibrotic lung disease.

Patients

Eligible patients were 40 years of age or older at the time of signing of informed consent; had a diagnosis of IPF on the basis of the 2018 clinical practice guideline of the American Thoracic Society and, if available, surgical lung-biopsy specimens; and had an FVC that was at least 45% of the predicted value.

Trial Procedures

Patients were randomly assigned at baseline in a 1:1 ratio to receive inhaled treprostinil or placebo. Randomization was stratified according to the use of IPF background therapy (nintedanib or pirfenidone vs. no background therapy). All the patients began receiving inhaled treprostinil or placebo at a dose of 3 breaths (18 µg) administered four times daily (during waking hours), and the dose was subsequently adjusted to reach a target of 12 breaths (72 µg) four times daily or the maximum clinically tolerated dose. Treprostinil inhalation solution or placebo was administered with the TD-300 ultrasonic nebulizer.

End Points

The primary end point was the change in absolute FVC from baseline to week 52.

Secondary efficacy end points were clinical worsening (including death from any cause, hospitalization due to a respiratory cause, or a relative decline of $\geq 10\%$ in the percentage of predicted FVC, whichever occurred first) and acute exacerbation of IPF, each assessed in a time-to-event analysis; death by week 52; the change from baseline in the percentage of predicted FVC at week 52 and quality of life.

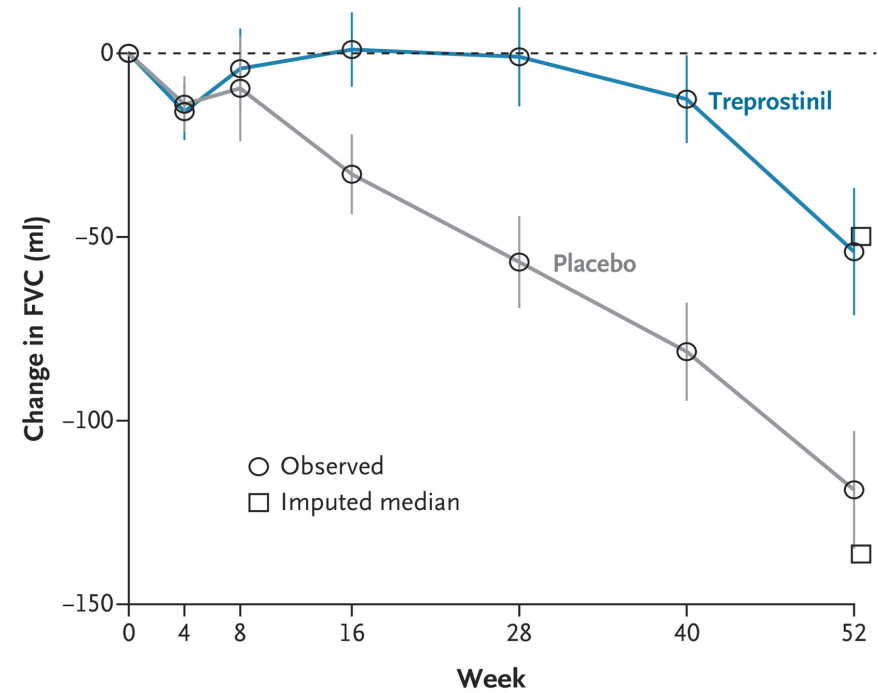
Characteristic	Treprostinil (N = 298)	Placebo (N = 295)	Total (N = 593)
Female sex — no. (%)	60 (20.1)	58 (19.7)	118 (19.9)
Age			
Mean (range) — yr	71.9 (41–91)	71.6 (50–88)	71.7 (41–91)
Distribution — no. (%)			
<65 yr	48 (16.1)	48 (16.3)	96 (16.2)
65 to <80 yr	209 (70.1)	215 (72.9)	424 (71.5)
≥80 yr	41 (13.8)	32 (10.8)	73 (12.3)
Race or ethnic group — no. (%) [†]			
White	262 (87.9)	235 (79.7)	497 (83.8)
Black or African American	0	1 (0.3)	1 (0.2)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	1 (0.2)
Asian	31 (10.4)	39 (13.2)	70 (11.8)
Multiple	0	1 (0.3)	1 (0.2)
Unknown	5 (1.7)	18 (6.1)	23 (3.9)
Hispanic or Latino ethnic group — no. (%) [†]			
Yes	85 (28.5)	74 (25.1)	159 (26.8)
No	202 (67.8)	203 (68.8)	405 (68.3)
Not reported	6 (2.0)	13 (4.4)	19 (3.2)
Unknown	5 (1.7)	5 (1.7)	10 (1.7)
Time since diagnosis of IPF — yr	4.02±3.01	3.74±2.62	3.88±2.83
Smoking status — no. (%)			
Never smoked	91 (30.5)	77 (26.1)	168 (28.3)
Current smoker	6 (2.0)	7 (2.4)	13 (2.2)
Former smoker	201 (67.4)	211 (71.5)	412 (69.5)
Use of supplemental oxygen — no. (%)	34 (11.4)	43 (14.6)	77 (13.0)
FVC			
Mean — ml	2683.7±737.8	2708.3±741.2	2695.9±739.0
Percentage of predicted value	76.4±17.7	77.2±17.3	76.8±17.5
Median NT-proBNP level (IQR) — pg/ml	90.5 (42.0–196.0)	84.0 (41.0–173.0)	85.0 (42.0–181.0)
DLco — % of predicted value	47.1±18.1	50.0±20.4	48.5±19.3
Background therapy — no. (%)			
None	73 (24.5)	73 (24.7)	146 (24.6)
Nintedanib	105 (35.2)	109 (36.9)	214 (36.1)
Pirfenidone	120 (40.3)	113 (38.3)	233 (39.3)

Primary and Secondary End Points.

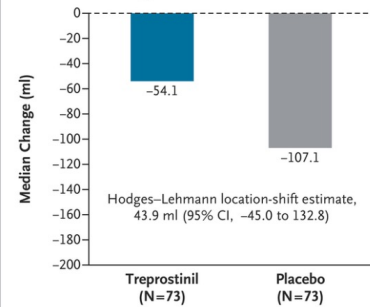
End Point	Treprostinil (N = 298)	Placebo (N = 295)	Hodges–Lehmann Estimate (95% CI) ^a	Hazard Ratio (95% CI) [†]
Primary end point				
Median estimated change in absolute FVC, baseline to week 52 (95% CI) — ml‡	–49.9 (–79.2 to –19.5)	–136.4 (–172.5 to –104.0)	95.6 (52.2 to 139.0)§	
Secondary end points				
Clinical worsening — no. of patients (%)¶				
Any clinical-worsening event	81 (27.2)	115 (39.0)		0.71 (0.53 to 0.95)‖
Death from any cause	4 (1.3)	3 (1.0)		
Hospitalization due to respiratory cause	30 (10.1)	38 (12.9)		
Relative decline of ≥10% in percentage of predicted FVC	47 (15.8)	74 (25.1)		
Exacerbation of IPF — no. of patients (%)	9 (3.0)	17 (5.8)		0.54 (0.24 to 1.22)
Death by week 52 — no. of patients (%)	19 (6.4)	24 (8.1)		0.77 (0.42 to 1.41)
Median estimated change in % of predicted FVC, baseline to week 52 (95% CI) — percentage points	–1.4 (–2.2 to –0.5)	–3.8 (–4.8 to –3.1)	2.7 (1.5 to 4.0)	
Median estimated change in K-BILD total score, baseline to week 52 (95% CI)‡***	–1.0 (–1.9 to 0.0)	–2.6 (–3.7 to –0.8)	2.3 (0.5 to 4.1)	
Median estimated change in % of predicted DLco, baseline to week 52 (95% CI) — percentage points‡	–2.8 (–4.1 to –2.0)	–4.1 (–5.5 to –3.2)	1.9 (0.1 to 3.8)	

Adverse Events.

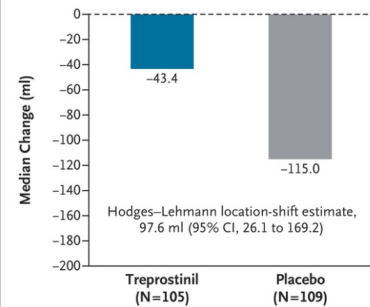
Event	Treprostinil (N = 298)	Placebo (N = 295)	Difference (95% CI) [†]
Adverse events			
No. of events	1558	1302	
No. of patients (%) with at least 1 event	273 (91.6)	264 (89.5)	ND
Serious adverse events			
No. of events	115	96	
No. of patients (%) with at least 1 event	75 (25.2)	68 (23.1)	ND
Adverse events leading to discontinuation of treprostinil or placebo			
No. of events	90	41	
No. of patients (%) with any adverse event leading to discontinuation	50 (16.8)	37 (12.5)	ND
Adverse events leading to death — no. of patients (%)	10 (3.4)	22 (7.5)	ND
Most common adverse events — no. of patients (%)			
Cough	144 (48.3)	71 (24.1)	24.3 (16.8 to 31.7)
Headache	59 (19.8)	35 (11.9)	7.9 (2.1 to 13.8)
Diarrhea	41 (13.8)	50 (16.9)	-3.2 (-9.0 to 2.6)
Dyspnea	36 (12.1)	31 (10.5)	1.6 (-3.5 to 6.7)
Bronchitis	30 (10.1)	30 (10.2)	-0.1 (-5.0 to 4.8)
Dizziness	29 (9.7)	19 (6.4)	3.3 (-1.1 to 7.7)
Worsening of IPF	28 (9.4)	37 (12.5)	-3.2 (-8.2 to 1.9)
Nasopharyngitis	25 (8.4)	30 (10.2)	-1.8 (-6.5 to 2.9)
Covid-19	25 (8.4)	22 (7.5)	0.9 (-3.4 to 5.3)
Nausea	24 (8.1)	26 (8.8)	-0.8 (-5.2 to 3.7)
Fatigue	23 (7.7)	20 (6.8)	0.9 (-3.2 to 5.1)
Throat irritation	21 (7.0)	7 (2.4)	4.7 (1.3 to 8.1)
Pneumonia	21 (7.0)	20 (6.8)	0.3 (-3.8 to 4.4)
Productive cough	21 (7.0)	8 (2.7)	4.3 (0.9 to 7.8)
Vomiting	20 (6.7)	16 (5.4)	1.3 (-2.6 to 5.1)
Respiratory tract infection	18 (6.0)	13 (4.4)	1.6 (-1.9 to 5.2)
Weight decrease	18 (6.0)	13 (4.4)	1.6 (-1.9 to 5.2)
Asthenia	18 (6.0)	14 (4.7)	1.3 (-2.3 to 4.9)
Influenza	16 (5.4)	17 (5.8)	-0.4 (-4.1 to 3.3)



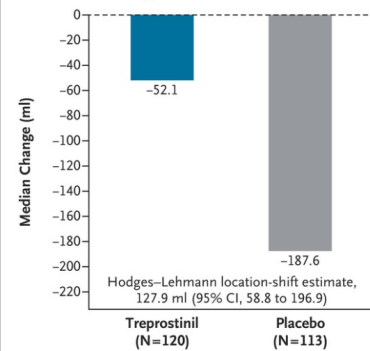
A Change in FVC among Patients not Receiving Background Antifibrotic Therapy



B Change in FVC among Patients Receiving Background Nintedanib Therapy

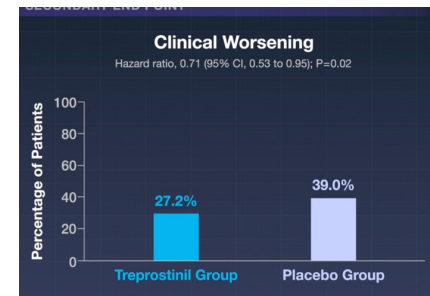
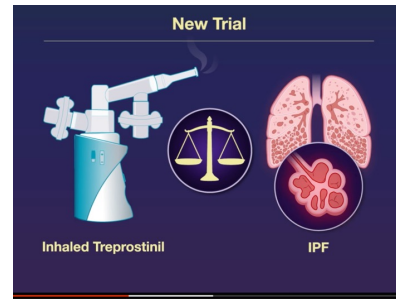
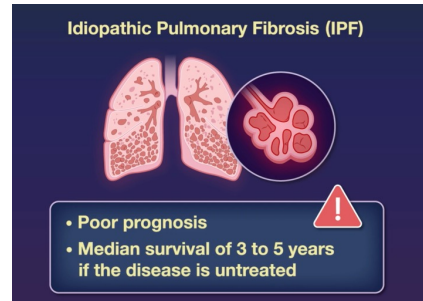


C Change in FVC among Patients Receiving Background Pirfenidone Therapy

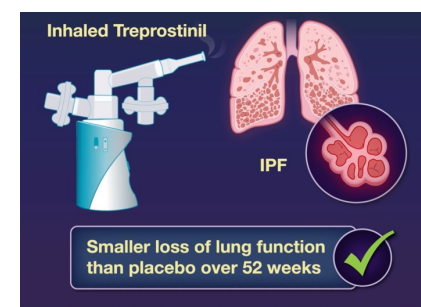
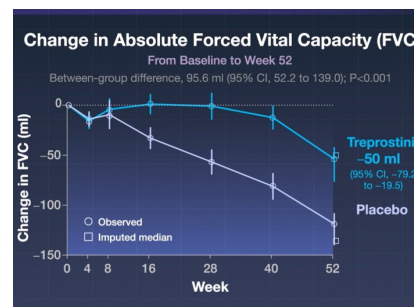
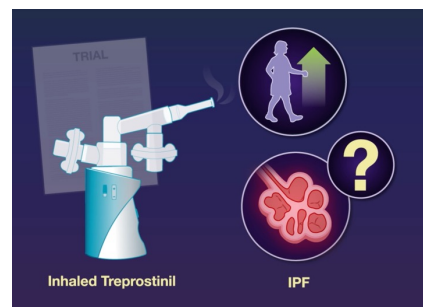
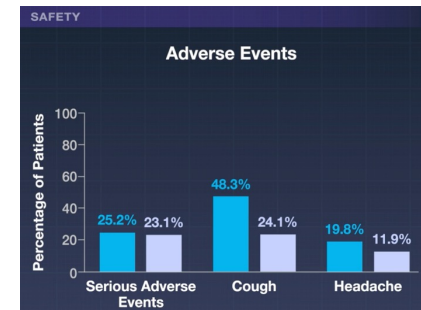
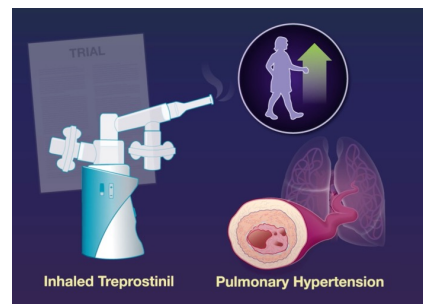


Change in Absolute FVC over a Period of 52 Weeks According to Use of Background Therapy.

The data shown are medians with imputed values. Confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.



Unfortunately, both got worse.



Der **Melanocortin-4-Rezeptor (MC4R)** ist ein Protein im menschlichen Gehirn (speziell im Hypothalamus), das als zentraler Schalter für **Sättigung und Energieverbrauch** dient. Die Aktivierung unterdrückt das Hungergefühl. Defekte in diesem Gen gelten als häufigste genetische Ursache für frühkindliches und starkes Übergewicht.

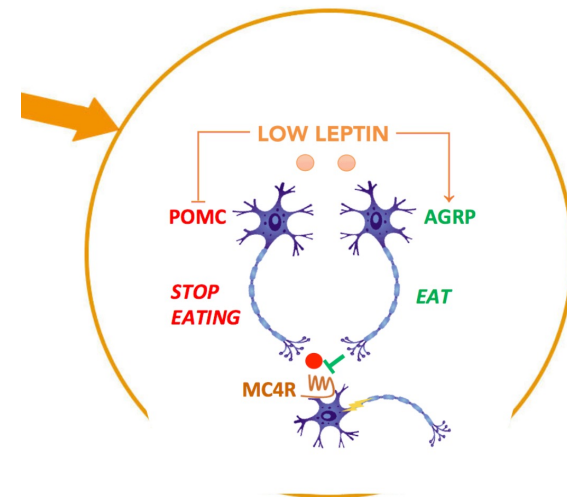
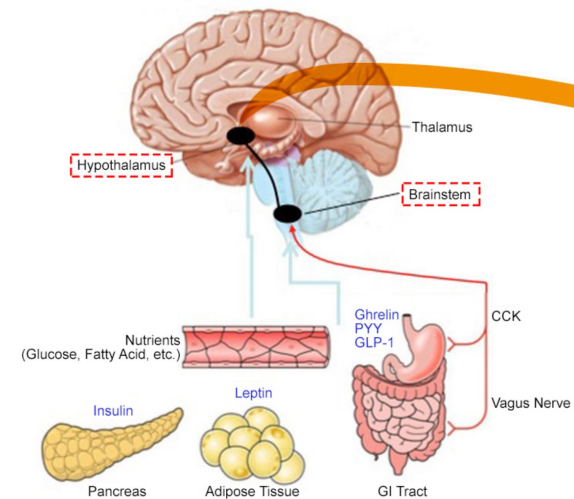
Der MC4R reguliert das Körpergewicht über komplexe neuronale Signalketten:

Funktion: Bindet das Hormon α -MSH an den MC4R, wird ein Sättigungssignal ausgelöst.

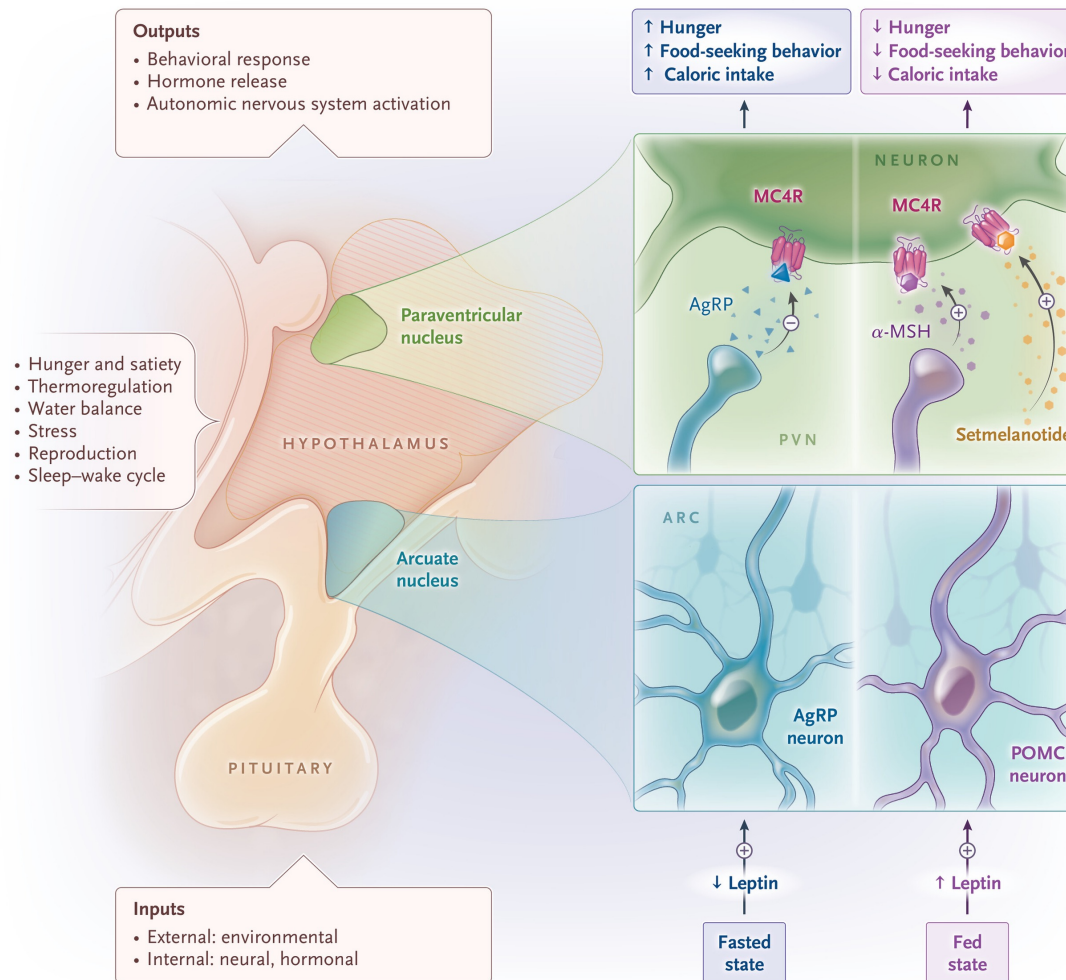
Gegenspieler: Das Peptid AgRP blockiert den Rezeptor und steigert den Appetit.

MC4R-Mangel: Ist der Rezeptor durch eine Mutation in seiner Funktion gestört, fehlt das natürliche Sättigungsgefühl. Dies führt zu *Hyperphagie* (ständigem, unstillbarem Hunger) und extremer Gewichtszunahme.

Besonderheit: Obwohl Betroffene oft stark adipös sind, zeigen manche Studien, dass sie genetisch bedingt oft bessere Blutfettwerte aufweisen als andere Adipositas-Patienten



Treating Acquired Hypothalamic Obesity



Regulation of Energy Homeostasis by the Hypothalamic Melanocortin Pathway.

Neurons in the hypothalamus respond to internal and external signals and alter pituitary hormone secretion, autonomic function, and behavior to maintain homeostasis. The melanocortin pathway involving pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons in the arcuate nucleus (ARC) and melanocortin 4 receptor (MC4R)-expressing neurons in the paraventricular nucleus (PVN) of the hypothalamus plays a critical role in weight regulation (zoomed-in view). POMC and AgRP neurons respond to peripheral hormonal signals such as leptin and project to multiple brain regions, including the PVN. Activation of MC4R by endogenous POMC-derived α -melanocyte-stimulating hormone (α -MSH) promotes satiety and reduces food-seeking behavior and food intake, whereas AgRP acts as an endogenous antagonist of MC4R, promoting food intake and opposing the effects of α -MSH. In acquired hypothalamic obesity, pharmacologic activation of MC4R by setmelanotide mimics the effects of α -MSH and improves pathway function.

Hyperphagia

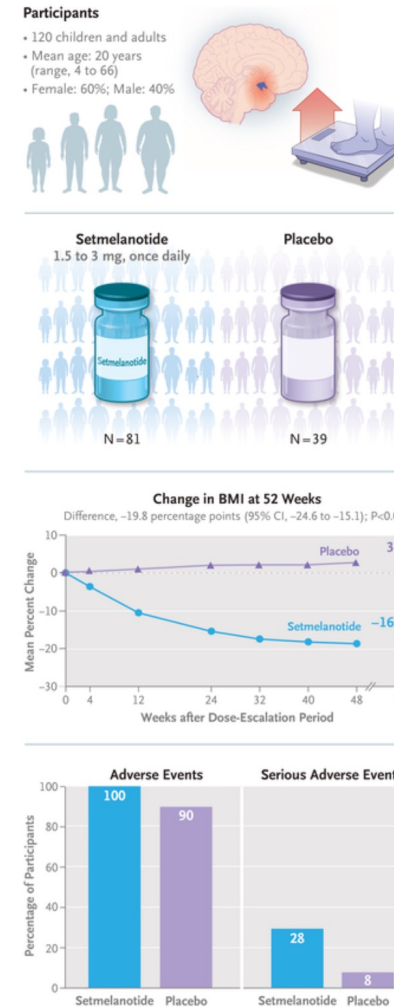
Excess eating due to increased hunger, impaired satiety (fullness after a meal), and increased food reward (liking or wanting food). Persistent hyperphagia is characterized by an intense drive to eat and is commonly accompanied by abnormal food-seeking behaviors (such as waking at night to seek food), preoccupation with food or food-related items, and distress when food is denied. It arises when the hypothalamic pathways that regulate eating behavior to maintain homeostasis and defend against starvation are disrupted by genetic or acquired conditions (e.g., tumors such as craniopharyngiomas).

Melanocortin 4 receptor (MC4R)

A G protein–coupled receptor expressed predominantly in the hypothalamus. MC4R is a key regulator of energy balance. Its ligands include peptide hormones derived from pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP): these peptides are secreted by neurons that respond to leptin and other hormonal signals reflecting nutritional status. In the fed state, activation of MC4R by α -melanocyte–stimulating hormone, which is derived from POMC, reduces food intake, whereas in the fasted state, AgRP inhibits MC4R signaling to increase food intake. Genetic variants that impair MC4R signaling cause obesity, whereas variants that enhance MC4R signaling confer protection against obesity.

Setmelanotide for the Treatment of Acquired Hypothalamic Obesity

A phase 2 trial of setmelanotide, a melanocortin-4 receptor agonist, showed substantial weight loss in patients with acquired hypothalamic obesity, but additional data are needed. We conducted a phase 3 trial in which participants were randomly assigned in a 2:1 ratio to receive setmelanotide (at a dose of 1.5 to 3.0 mg) or placebo administered subcutaneously once daily for 52 weeks after a dose-escalation period. Persons at least 4 years of age were potentially eligible for the trial if they had acquired hypothalamic obesity, which was defined by a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) that was at or above the 95th percentile for age and sex (for participants <18 years of age) or at least 30 (for participants ≥18 years of age) and a history of a hypothalamic tumor, lesion, or injury. The primary end point was the mean percent change in BMI from baseline to 52 weeks after the end of the dose-escalation period. Secondary end points included the mean change in the weekly average of the maximal daily hunger score (range, 0 to 10, with higher scores indicating more severe hunger), assessed in participants at least 12 years of age.



Acquired hypothalamic obesity is characterized by accelerated and sustained weight gain in the context of broad hypothalamic impairment after hypothalamic injury or disease, such as in cases of suprasellar tumors (or their surgical resection), traumatic brain injury, inflammation, or a combination of these conditions. Commonly observed symptoms in acquired hypothalamic obesity include hyperphagia, pituitary hormone deficiencies, fatigue, sleep disturbances, body temperature dysregulation, reduced resting energy expenditure, and energy imbalance.

The melanocortin-4 receptor (MC4R) pathway originates in the hypothalamus and extends to the brain stem and spinal cord; this pathway has a critical role in homeostatic control of body weight through regulation of hunger and satiety, food consumption, and energy expenditure. Anatomical disruption of this pathway in acquired hypothalamic obesity may impair the expression of α -melanocyte-stimulating hormone (α -MSH), with this impairment potentially leading to increased hunger. Hyperphagia, a feeling of insatiable hunger and a severe preoccupation with food that is accompanied by abnormal food-seeking behaviors, develops in approximately 72% of patients with acquired hypothalamic obesity.

Setmelanotide is a functional analogue of the endogenous ligand α -MSH and is approved for the treatment of diseases associated with impaired MC4R signaling.

Participants

Eligible participants were at least 4 years of age and had a diagnosis of craniopharyngioma or another brain lesion affecting the hypothalamic region, for which they had undergone surgery, chemotherapy, or radiation therapy involving the hypothalamus at least 6 months before screening, or had had documented injury to the hypothalamus at least 6 months before screening, for which surgery or radiation was not indicated.

Procedures

Participants were randomly assigned in a 2:1 ratio to receive setmelanotide at a therapeutic dose (1.5 to 3.0 mg) or placebo for 52 weeks after the dose-escalation period; the entire treatment period (including the dose-escalation period) was approximately 60 weeks.

End Points and Assessments

The primary end point was the mean percent change in BMI from baseline to the end of the treatment period (52 weeks after the completion of the dose-escalation period). Key secondary end points included a reduction in BMI of at least 5% among participants 18 years of age or older or a reduction in the BMI z score of at least 0.2 points.

Characteristic	Setmelanotide (N = 81)	Placebo (N = 39)
Age		
Mean — yr	19.2±13.0	21.4±15.5
Range — yr	4–65	4–66
Distribution — no. (%)		
<18 yr	48 (59)	23 (59)
≥18 yr	33 (41)	16 (41)
Sex — no. (%)		
Female	45 (56)	27 (69)
Male	36 (44)	12 (31)
Race — no. (%)†		
White	66 (81)	34 (87)
Black	6 (7)	0
Asian	3 (4)	0
Other	6 (7)	5 (13)
Hispanic or Latino ethnic group — no. (%)†		
Yes	7 (9)	7 (18)
No	73 (90)	32 (82)
Unknown	1 (1)	0
Type of tumor or other cause of damage to hypothalamus — no. (%)		
Craniopharyngioma	63 (78)	30 (77)
Glioma	4 (5)	3 (8)
Astrocytoma	3 (4)	3 (8)
Germinoma	5 (6)	1 (3)
Hamartoma	1 (1)	1 (3)
Other non-tumor-related cause	5 (6)‡	1 (3)§
Weight — kg		
All participants	92.9±38.5	94.1±38.8
Participants ≥18 yr of age	115.6±33.8	124.2±32.9
BMI¶		
All participants	35.7±9.2	36.8±9.3
Participants ≥18 yr of age	40.1±9.8	43.5±9.3
BMI z score in participants 4 to <18 yr of age	3.72±1.81	3.37±1.29
Percentage of 95th-percentile BMI in participants 4 to <18 yr of age**	132.3±28.9	128.6±22.7
Waist circumference — cm	106.6±21.7	108.6±18.8
Maximal daily hunger score in participants ≥12 yr of age††	6.77±2.32	7.23±2.11

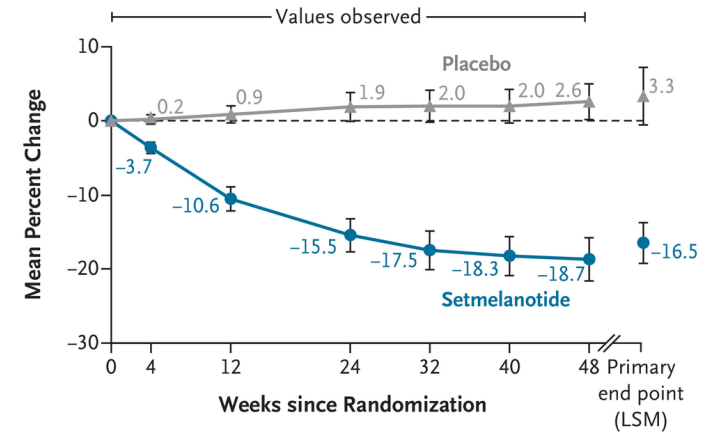
Primary and Secondary End Points.

End Point	Setmelanotide (N=81)		Placebo (N=39)		Treatment Difference†	P Value
	No. Evaluated/ No. Eligible	Value (95% CI)	No. Evaluated/ No. Eligible	Value (95% CI)		
Primary end point						
Mean change in BMI — %‡	81/81	–16.5 (–19.3 to –13.8)	39/39	3.3 (–0.6 to 7.2)	–19.8 (–24.6 to –15.1)	<0.001
Key secondary end points						
Reduction in BMI of ≥5% or in BMI z score of ≥0.2 — % of participants‡§	81/81	83 (74 to 91)	39/39	21 (8 to 34)	62 (48 to 77)	<0.001
Reduction in BMI of ≥5% — % of participants‡	81/81	80 (71 to 88)	39/39	10 (1 to 20)	69 (56 to 82)	<0.001
Change in maximal daily hunger score in participants ≥12 yr of age — points¶	57/61	–2.73 (–3.28 to –2.18)	24/28	–1.45 (–2.23 to –0.67)	–1.28 (–2.23 to –0.33)	0.009
Other hunger-based secondary end points						
Reduction of ≥2 points in maximal daily hunger score in participants ≥12 yr of age — % of participants¶	57/61	61 (47 to 75)	24/28	45 (25 to 66)	16 (–9 to 41)	—
Change in Symptoms of Hyperphagia composite score — points 						
Score based on caregiver report	23/26	–0.65 (–0.83 to –0.48)	11/14	–0.24 (–0.46 to –0.03)	–0.41 (–0.62 to –0.20)	—
Score based on participant report	33/55	–0.30 (–0.36 to –0.25)	16/25	–0.14 (–0.23 to –0.06)	–0.16 (–0.27 to –0.06)	—
Other weight-based secondary end points						
Change in weight in participants ≥18 yr of age — kg	33/33	–16.5 (–21.0 to –12.0)	16/16	2.4 (–3.9 to 8.8)	–19.0 (–26.7 to –11.2)	—
Change in BMI z score in participants <18 yr of age — points**	45/48	–1.47 (–1.72 to –1.22)	23/23	–0.12 (–0.47 to 0.23)	–1.35 (–1.79 to –0.92)	—
Change in percentage of 95th-percentile BMI in participants <18 yr of age — percentage points††	48/48	–26.3 (–30.8 to –21.8)	23/23	–0.1 (–6.6 to 6.3)	–26.2 (–34.0 to –18.3)	—
Other secondary end points						
Change in IWQOL-Lite-CT scores — points‡‡						
Total score	25/33	32.0 (25.8 to 38.3)	13/16	3.0 (–5.6 to 11.6)	29.0 (18.4 to 39.7)	—
Physical Function score	25/33	31.3 (23.8 to 38.8)	13/16	–4.5 (–14.9 to 6.0)	35.8 (22.9 to 48.7)	—
Change in IWQOL-Kids total score — points§§	17/25	22.1 (12.3 to 31.8)	11/12	7.9 (–0.3 to 16.2)	14.1 (5.4 to 22.9)	—
Change in waist circumference (95% CI) — cm	71/81	–11.6 (–13.9 to –9.3)	37/39	3.9 (0.7 to 7.0)	–15.4 (–19.3 to –11.6)	—
Cardiometabolic secondary end points						
Change in blood pressure — mm Hg						
Systolic	73/81	–2.8 (–5.2 to –0.3)	37/39	3.0 (–0.5 to 6.4)	–5.7 (–10.0 to –1.5)	—
Diastolic	73/81	–1.3 (–2.9 to 0.4)	37/39	2.8 (0.5 to 5.1)	–4.1 (–6.9 to –1.2)	—
Change in cholesterol levels — mmol/liter						
Total cholesterol	67/81	–0.2 (–0.4 to 0.0)	36/39	0.2 (–0.1 to 0.5)	–0.4 (–0.7 to –0.1)	—
LDL cholesterol	66/81	–0.3 (–0.5 to –0.1)	34/39	0.1 (–0.1 to 0.3)	–0.4 (–0.7 to –0.1)	—
HDL cholesterol	66/81	0.4 (0.3 to 0.5)	35/39	0.1 (0.0 to 0.2)	0.3 (0.1 to 0.4)	—
Change in glycated hemoglobin level — percentage points	67/81	–0.3 (–0.3 to –0.2)	35/39	0.0 (–0.1 to 0.1)	–0.3 (–0.4 to –0.1)	—
Change in triglyceride level — mmol/liter	67/81	–0.6 (–0.8 to –0.4)	36/39	0.0 (–0.3 to 0.2)	–0.6 (–0.9 to –0.3)	—
Change in liver-enzyme levels — U/liter						
Aspartate aminotransferase	66/81	–6.4 (–9.8 to –3.0)	35/39	1.1 (–3.5 to 5.7)	–7.5 (–13.2 to –1.8)	—
Alanine aminotransferase	65/81	–13.9 (–20.1 to –7.8)	35/39	0.9 (–7.4 to 9.3)	–14.9 (–25.2 to –4.6)	—
Change in bilirubin level — μmol/liter	66/81	1.5 (0.4 to 2.6)	35/39	0.1 (–1.5 to 1.6)	1.4 (–0.5 to 3.3)	—
Change in C-reactive protein level — mg/liter	60/81	–2.5 (–4.3 to –0.7)	29/39	0.5 (–2.1 to 3.1)	–3.0 (–6.1 to 0.2)	—

Safety.

Event	Setmelanotide (N=81)	Placebo (N=39)
	<i>number of participants (percent)</i>	
Any adverse event	81 (100)	35 (90)
Any adverse event leading to discontinuation of the trial regimen	6 (7)	3 (8)
Any adverse event leading to withdrawal from the trial	4 (5)	0
Any serious adverse event	23 (28)	3 (8)
Any adverse event resulting in death during the trial	1 (1)	0
Adverse events that occurred in ≥10% of participants receiving setmelanotide		
Skin hyperpigmentation	45 (56)	3 (8)
Nausea	41 (51)	12 (31)
Vomiting	32 (40)	7 (18)
Headache	31 (38)	12 (31)
Injection-site reaction	19 (23)	9 (23)
Diarrhea	19 (23)	8 (21)
Injection-site pruritus	15 (19)	8 (21)
Upper respiratory tract infection	15 (19)	5 (13)
Injection-site erythema	14 (17)	4 (10)
Melanocytic nevus	14 (17)	2 (5)
Abdominal pain	12 (15)	5 (13)
Cough	11 (14)	6 (15)
Covid-19	11 (14)	5 (13)
Fatigue	10 (12)	4 (10)
Constipation	10 (12)	2 (5)
Dizziness	9 (11)	2 (5)
Oropharyngeal pain	9 (11)	1 (3)
Any adverse event related to the trial regimen†	71 (88)	26 (67)
Any serious adverse event related to the trial regimen†	1 (1)	0

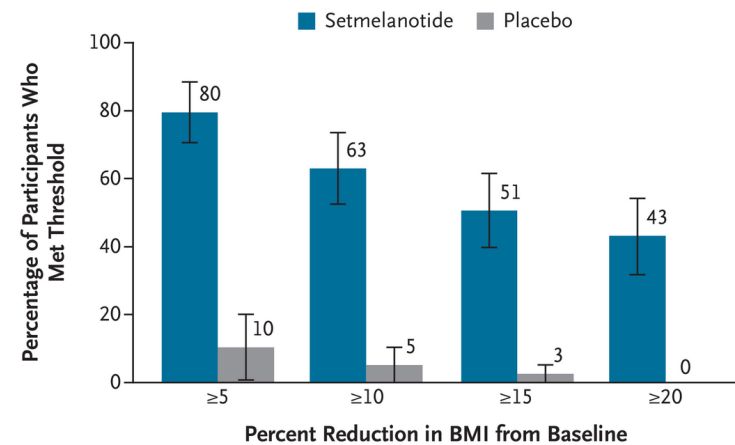
A Percent Change in BMI over Time

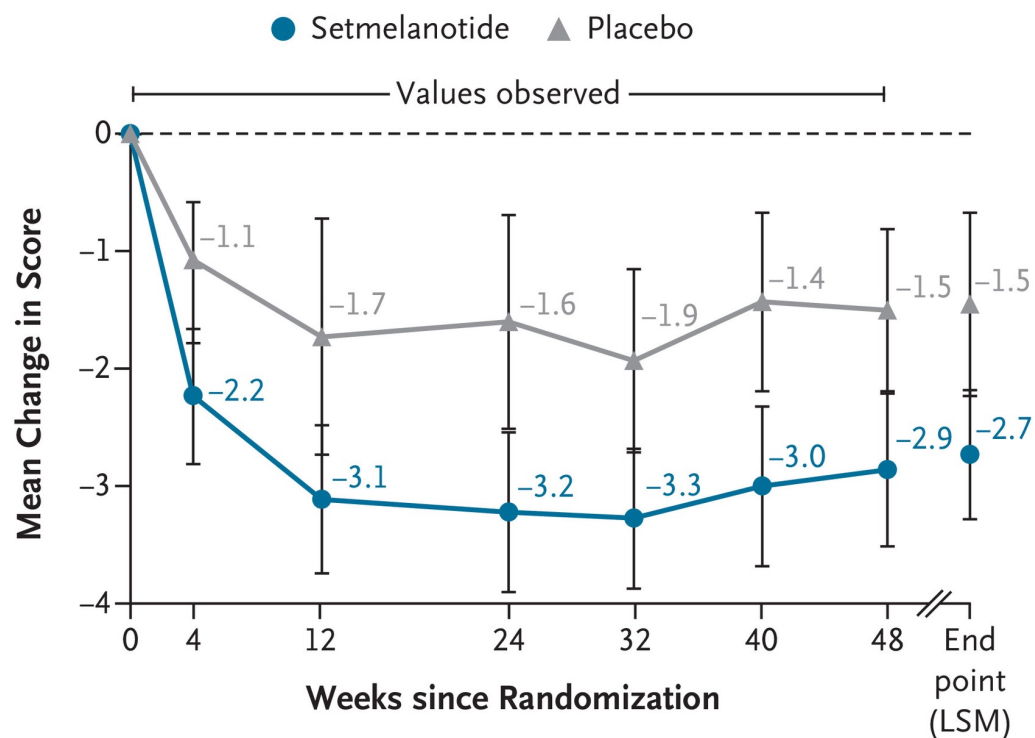


No. of Participants

Placebo	39	38	37	38	34	36	33	39
Setmelanotide	81	81	77	75	68	73	68	81

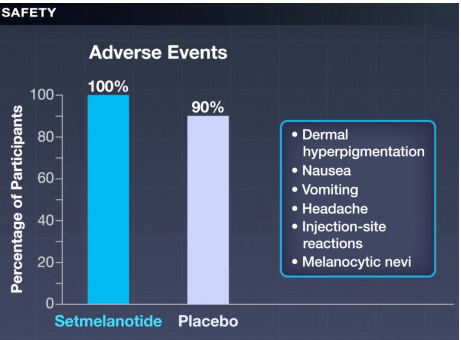
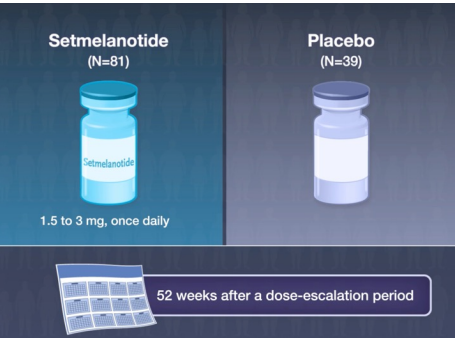
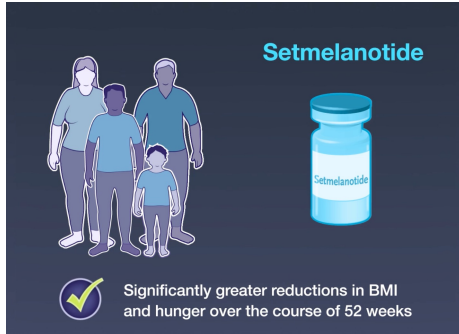
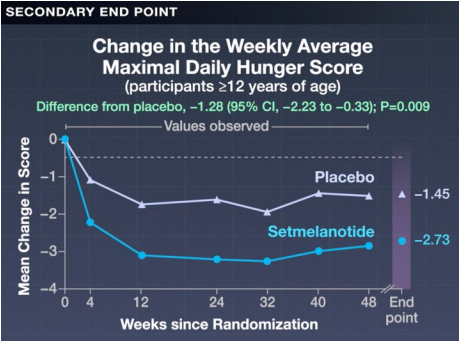
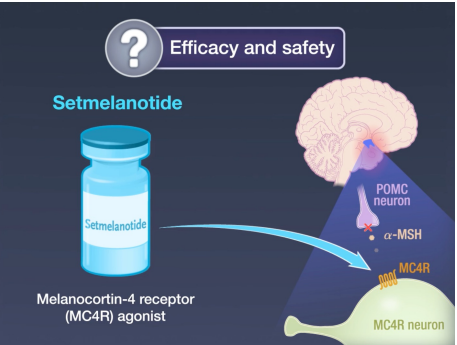
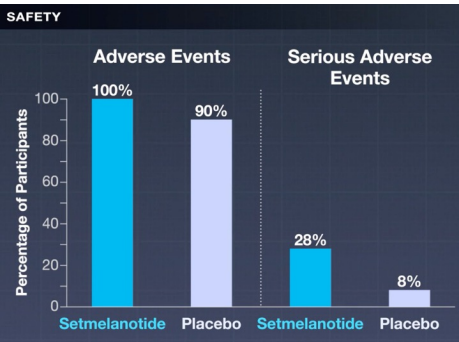
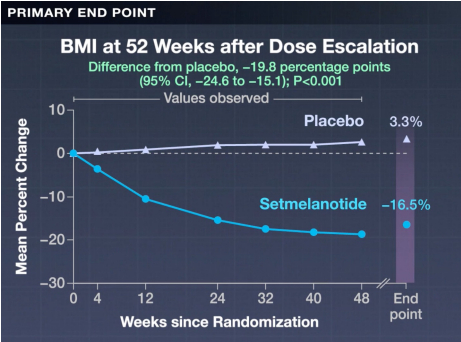
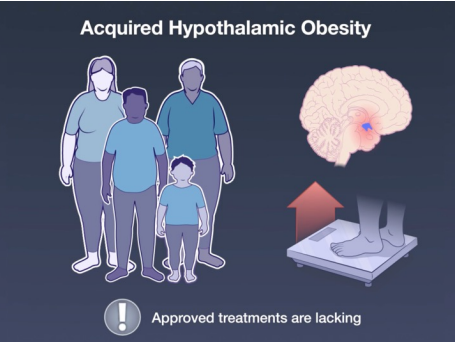
B Thresholds of BMI Reduction





Effects of Once-Daily Setmelanotide on Weekly Average of Maximal Daily Hunger Scores.

Primary analyses were performed at 52 weeks after the end of the dose-escalation period. Shown is the mean change in the maximal daily hunger score by visit among participants at least 12 years of age who were able to assess and report their scores. Values shown are observed values up to 48 weeks after randomization, and LSM values are shown at 52 weeks after the end of the dose-escalation period (the end point). Hunger was scored on an 11-point numerical rating scale from 0 (not hungry at all) to 10 (hungriest possible). I bars indicate 95% confidence intervals.



Melanocortin-4 receptor (MC4R) agonists are primarily designed to treat rare genetic and acquired forms of obesity characterized by severe hyperphagia (uncontrollable hunger) and pathway impairment. In generally obese persons, they are **not typically effective** and are not FDA-approved for standard, diet-induced obesity.

The MC4R is located in the hypothalamus and serves as a central regulator of appetite and energy expenditure.

- Genetic Deficiencies:** In rare conditions like POMC, PCSK1, or LEPR deficiencies, the signaling pathway to the MC4R is broken. Drugs like setmelanotide bypass these defects to directly stimulate the receptor, turning off extreme hunger and facilitating significant weight loss.

- Acquired Hypothalamic Obesity:** MC4R agonists are also utilized for patients who suffer from obesity caused by hypothalamic tumors, lesions, or traumatic brain injuries.

Why They Fail in General Obesity

For the vast majority of people with general (non-monogenic) obesity, the MC4R signaling pathway is already fully functional.

- Diminished Returns:** Because the receptor is already receiving normal signals from the body's natural hormones, adding an external MC4R agonist does not trigger any extra weight loss.

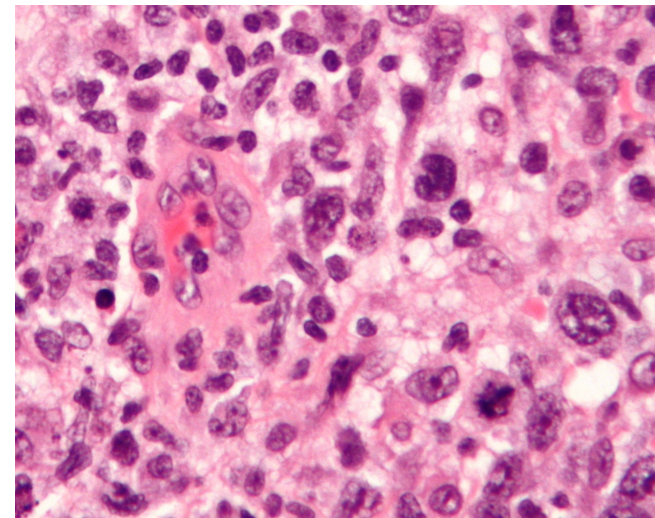
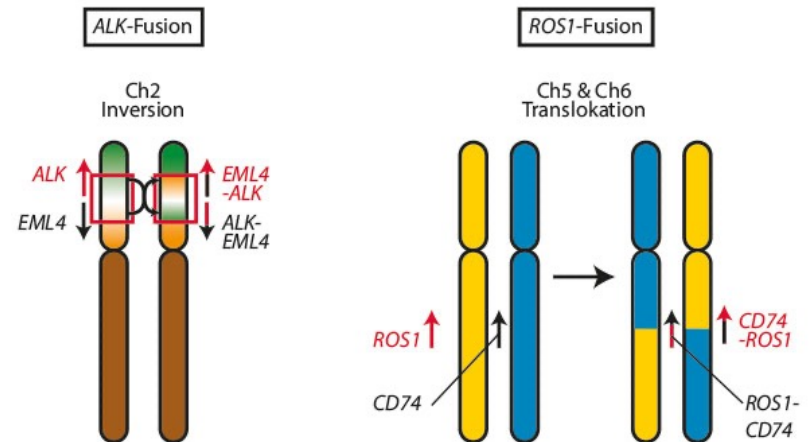
- Historical Challenges:** In the early 2000s, pharmaceutical companies tested several broad-spectrum MC4R agonists for general obesity but abandoned them due to a lack of meaningful weight loss and severe side effects, such as dangerous increases in heart rate and blood pressure.

Die **anaplastische Lymphomkinase (ALK)** ist ein körpereigenes Protein und Enzym aus der Gruppe der Rezeptor-Tyrosinkinasen, das eine **zentrale Rolle bei der Entstehung und gezielten Behandlung bestimmter Krebserkrankungen** spielt. Während das zugrundeliegende ALK-Gen bei gesunden Erwachsenen fast vollständig abgeschaltet ist, führt eine genetische Veränderung (Mutation oder Fusion) in Krebszellen dazu, dass das Enzym dauerhaft aktiv bleibt und unkontrolliertes Tumorstwachstum antreibt.

Normalzustand: In der Embryonalentwicklung steuert ALK das Wachstum und die Entwicklung von Nervenzellen. Nach der Geburt verliert es seine aktive Funktion weitgehend.

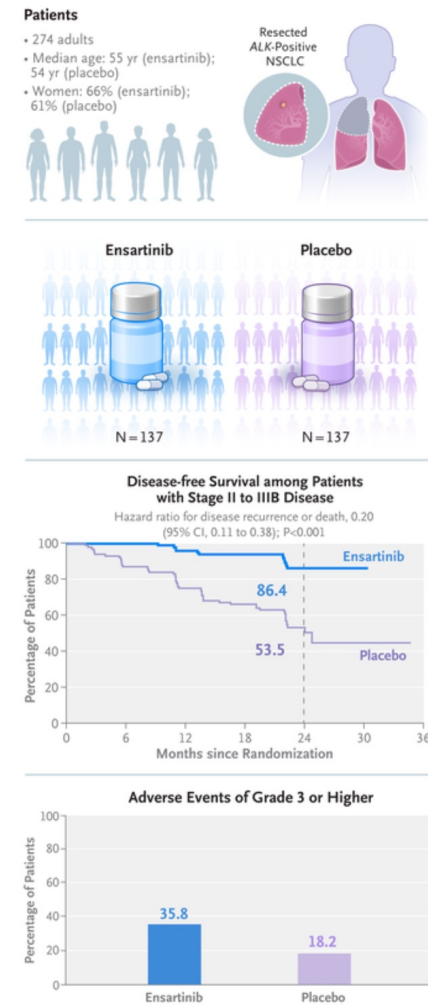
Die Krebs-Fusion: Durch einen Fehler in der DNA bricht das ALK-Gen auf und verschmilzt mit einem Nachbargenen (häufig dem EML4-Gen).

Dauer-Signal: Diese Fusion erschafft ein verändertes Protein, das wie ein defekter Lichtschalter dauerhaft auf „An“ steht. Es sendet ununterbrochen Signale zur Zellteilung an die Zelle, wodurch ein Tumor entsteht.



Ensartinib in Resected ALK-Positive Non–Small-Cell Lung Cancer

Anaplastic lymphoma kinase (ALK) inhibitors have emerged as promising agents for patients with resectable *ALK*-positive non–small-cell lung cancer (NSCLC). Whether ensartinib, a second-generation ALK inhibitor, is safe and effective in such patients is unknown. In this phase 3, double-blind, randomized trial involving patients with completely resected, *ALK*-positive stage IB to IIIB NSCLC after adjuvant chemotherapy, we randomly assigned patients in a 1:1 ratio to receive ensartinib at a dose of 225 mg once daily or placebo for 24 months. The primary end point was disease-free survival in patients with stage II to IIIB NSCLC. The key secondary end point was disease-free survival in the overall patient population.



Approximately 30% of patients with non–small-cell lung cancer (NSCLC) are eligible for potentially curative resection. Nevertheless, even after surgical resection, patients remain at risk for postoperative recurrence and death. Adjuvant chemotherapy is recommended for patients with completely resected pathological stage IB NSCLC with high-risk features (node-positive, or node-negative with a primary tumor size of ≥ 4 cm) and for patients with stage II to IIIB tumors. In contrast, adjuvant radiotherapy is no longer routinely recommended for patients with postoperative N2 disease.

ALK rearrangement occurs in 5% of patients with NSCLC and is more common among younger patients and those who never smoked. Patients with advanced *ALK*-positive NSCLC are at high risk for development of central nervous system (CNS) metastases. Despite the recent approval of immunotherapy for the treatment of resectable NSCLC, clinical evidence that immunotherapy is beneficial in NSCLC with oncogenic driver alterations is limited.

Ensartinib is an oral, potent *ALK* inhibitor that has been shown to have robust efficacy and a favorable safety profile in patients with advanced or metastatic NSCLC.

Patients

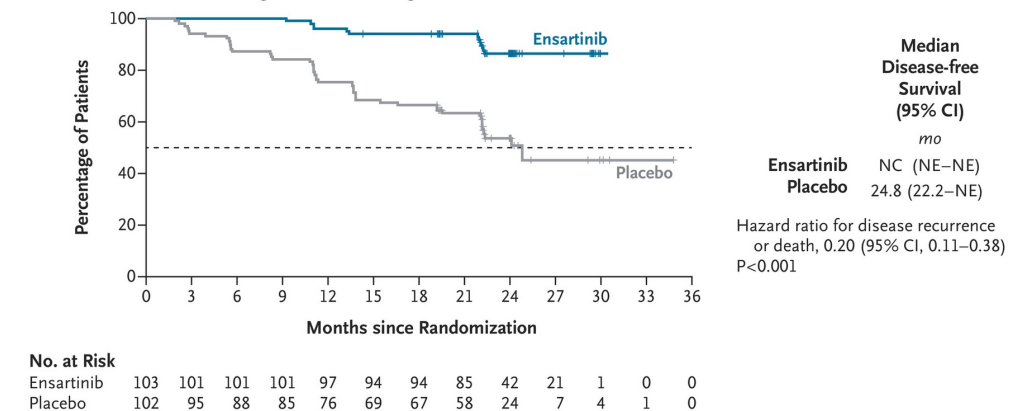
Eligible patients were 18 years of age or older, had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (range, 0 to 5, with higher scores indicating greater disability), and had histologically confirmed, completely resected stage IB, II, IIIA, or IIIB NSCLC. Eligible patients were randomly assigned in a 1:1 ratio to receive oral ensartinib at a dose of 225 mg once daily or placebo after complete surgical resection (lobectomy, segmentectomy, bilobectomy, or pneumonectomy) and any planned adjuvant chemotherapy.

End Points and Assessments

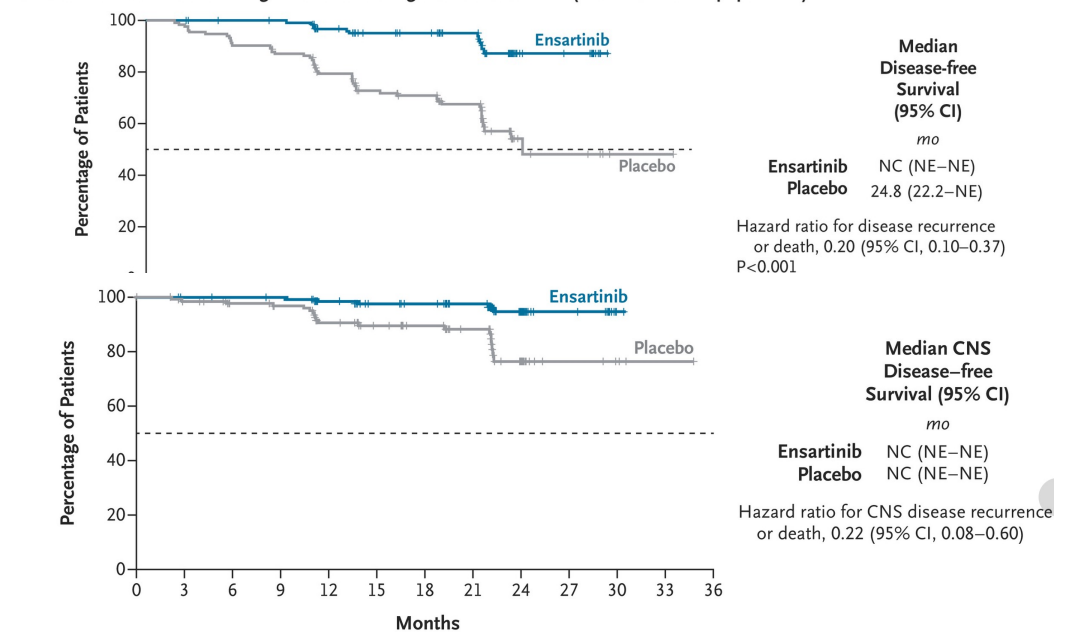
The primary end point was investigator-assessed disease-free survival, defined as the time from randomization to disease recurrence or death from any cause, in patients with stage II to IIIB disease. The key secondary end point was disease-free survival in the overall patient population with stage IB to IIIB disease.

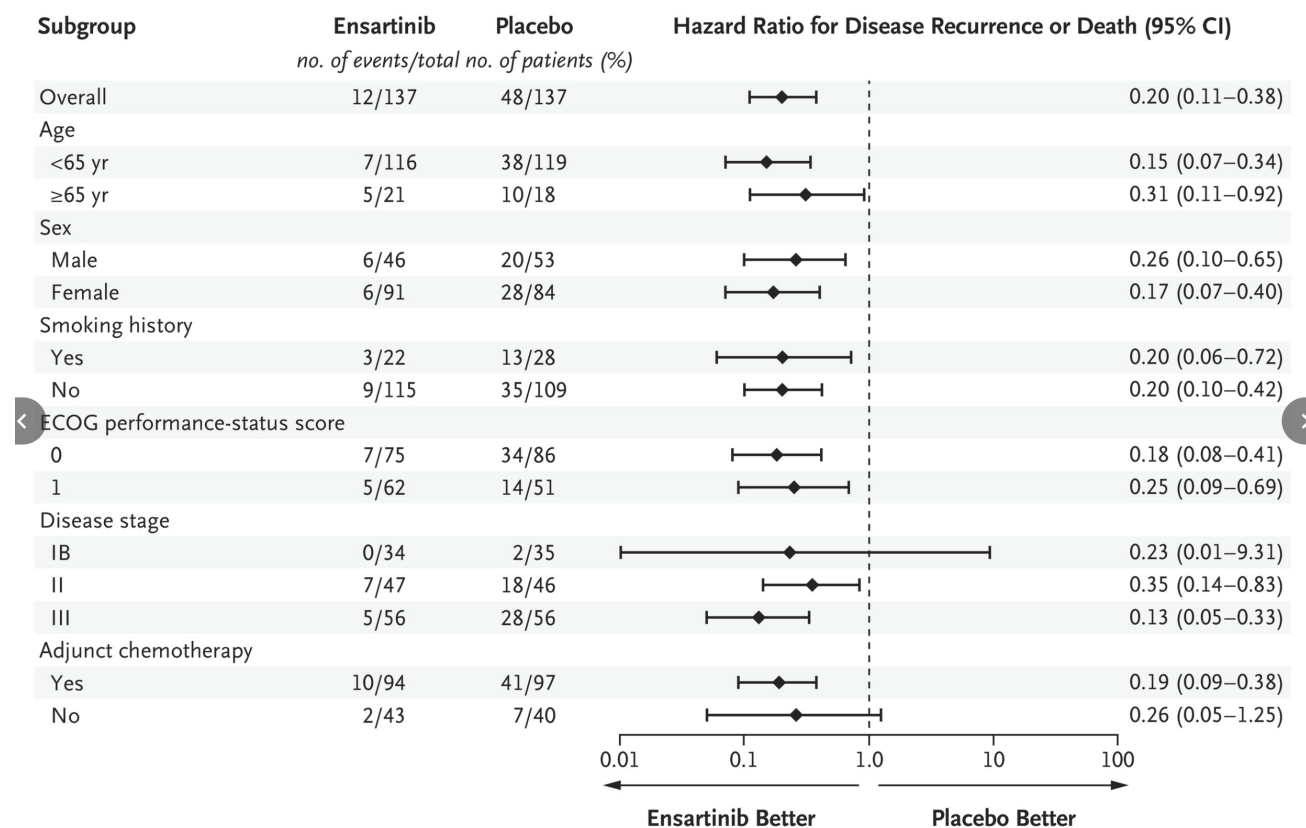
Characteristic	Ensartinib (N = 137)	Placebo (N = 137)
Age — yr		
Median	55	54
Range	25–78	20–74
Sex — no. (%)		
Female	91 (66.4)	84 (61.3)
Male	46 (33.6)	53 (38.7)
ECOG performance-status score — no. (%) [†]		
0	75 (54.7)	86 (62.8)
1	62 (45.3)	51 (37.2)
Smoking history — no. (%)		
Never smoked	115 (83.9)	109 (79.6)
Former smoker	21 (15.3)	27 (19.7)
Current smoker	1 (0.7)	1 (0.7)
Disease stage — no. (%) [‡]		
IB	34 (24.8)	35 (25.5)
II	47 (34.3)	46 (33.6)
III	56 (40.9)	56 (40.9)
Histologic type — no. (%)		
Squamous	1 (0.7)	2 (1.5)
Nonsquamous	136 (99.3)	135 (98.5)
Resection type — no. (%)		
Lobectomy	125 (91.2)	130 (94.9)
Bilobectomy	8 (5.8)	3 (2.2)
Pneumonectomy	1 (0.7)	1 (0.7)
Segmentectomy	3 (2.2)	3 (2.2)
Adjuvant chemotherapy — no. (%)		
Yes	94 (68.6)	97 (70.8)
No	43 (31.4)	40 (29.2)

A Disease-free Survival among Patients with Stage II to IIIB Disease



B Disease-free Survival among Patients with Stage IB to IIIB Disease (intention-to-treat population)

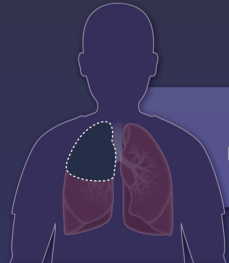




Subgroup Analysis of Disease-free Survival.

The hazard ratio and 95% confidence interval for stage IB subgroup were estimated with a penalized Cox model (Firth's method).

Resected ALK-Positive Non-Small-Cell Lung Cancer



At risk for
postoperative
recurrence

ELEVATE Trial

- Ongoing
- Phase 3
- Double-blind
- Randomized
- Placebo-controlled

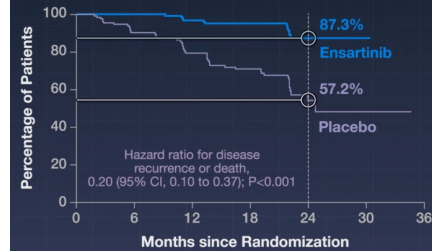
274 Patients

- With completely resected, stage IB to IIIB ALK-positive NSCLC
- Had previously undergone adjuvant chemotherapy

KEY SECONDARY END POINT

Disease-free Survival

Overall population (patients with stage IB to IIIB disease)

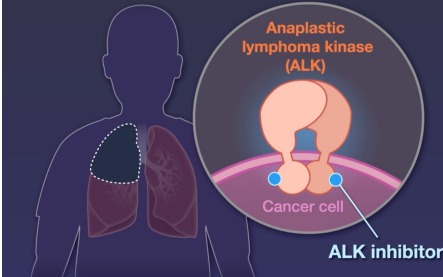


Resected Stage IB to IIIB ALK-positive Non-Small-Cell Lung Cancer



The percentage of patients who were alive and disease-free at 24 months was significantly higher with ensartinib than with placebo

Resected ALK-Positive Non-Small-Cell Lung Cancer



Oral Ensartinib



N=137

Placebo

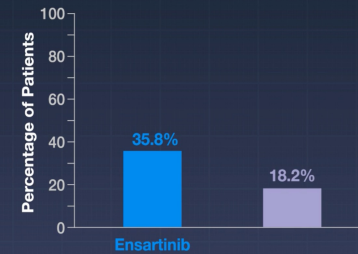


N=137

Once daily for up to 24 months

ADVERSE EVENTS

Grade ≥3 Adverse Events



Resected ALK-Positive Non-Small-Cell Lung Cancer

Efficacy and Safety

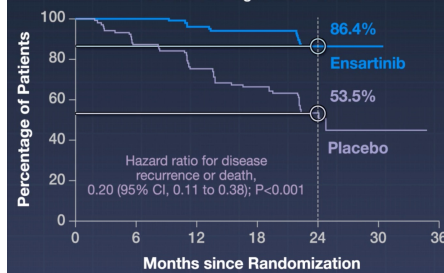


VS



Disease-free Survival

Patients with stage II to IIIB disease



ADVERSE EVENTS

Grade ≥3 Adverse Events

Rash



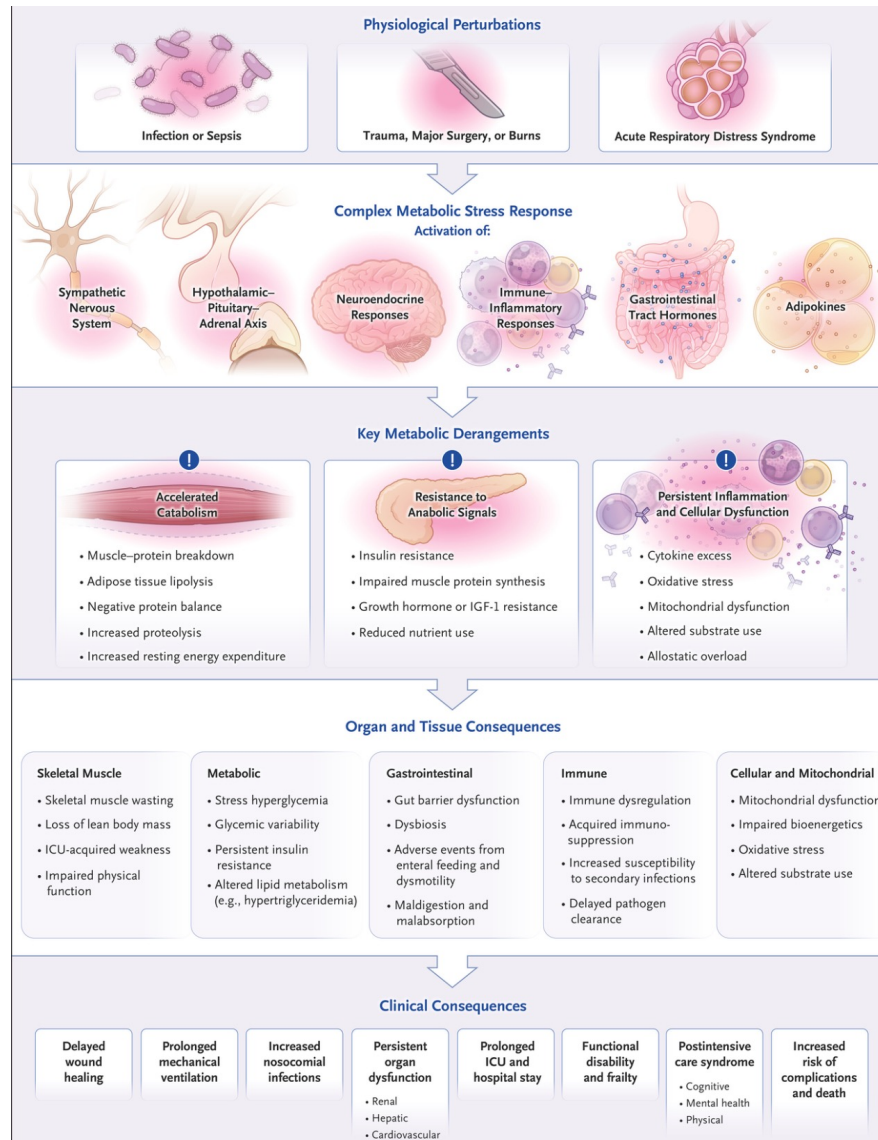
Nutrition Therapy in Critically Ill Adults

Summary

In the acute phase of critical illness, adults have severe catabolism, inflammation, muscle loss, and gut dysfunction, all of which shape nutritional requirements. Early enteral nutrition supports gut integrity and microbiome health, but trials have shown that early short-term parenteral nutrition is a safe alternative when enteral feeding is not possible. Large trials have shown that **early full-dose energy delivery offers no benefit** over restrictive dosing and may increase gastrointestinal and metabolic complications, findings that support a restrictive nutrition strategy, especially in patients who have circulatory shock or are at risk for refeeding syndrome. Similarly, large trials have shown **no advantage of high-dose over standard-dose protein** and suggest harm in patients with acute kidney injury. Because adverse events are common with enteral nutrition, safe nutrition delivery requires gradual advancement, strategies for prevention of refeeding syndrome, glycemic control, and avoidance of routine gastric residual volume monitoring. Patient heterogeneity underscores the need for precise, biomarker-guided, phase-specific nutrition to preserve lean muscle mass and improve recovery.

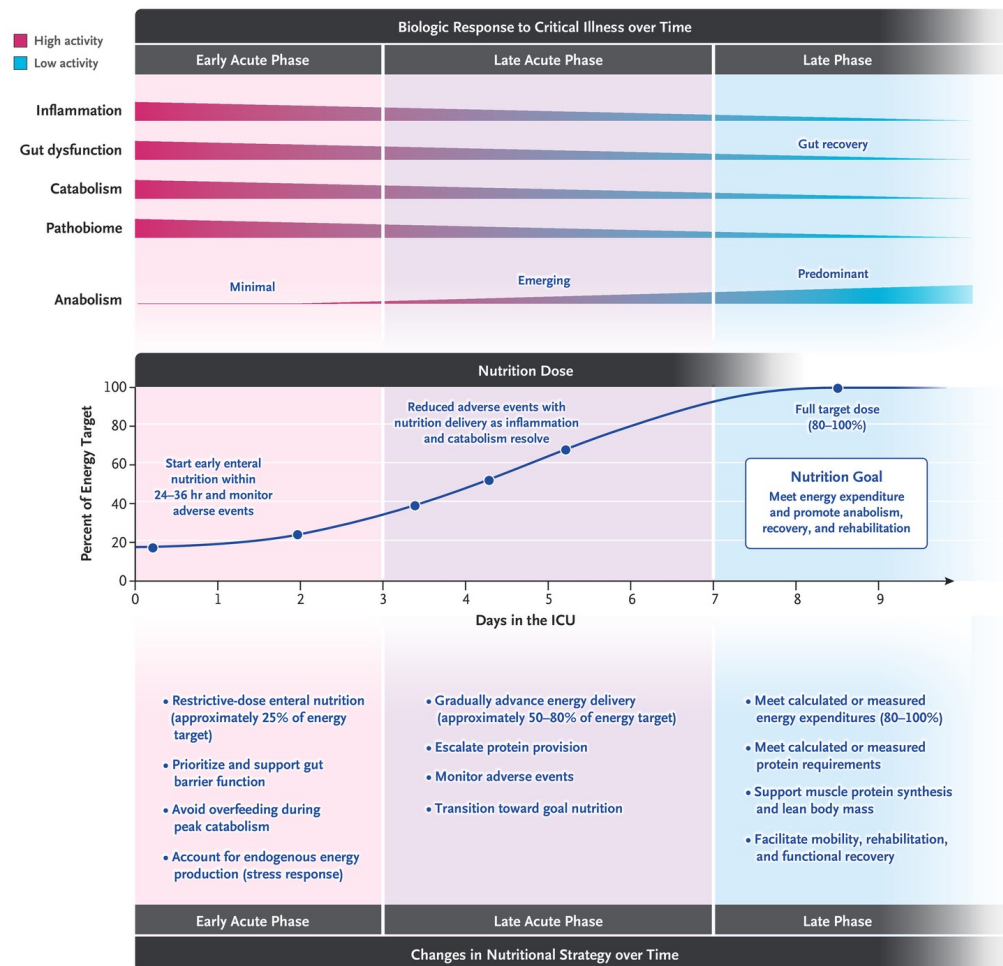
Nutrition Therapy in Critically Ill Adults

- The acute phase of critical illness is marked by intense catabolism, inflammation, rapid skeletal muscle loss, and gut dysfunction.
- Early enteral nutrition preserves gut integrity and supports the microbiome, so it is the preferred approach, although contemporary randomized, controlled trials show that early short-term parenteral nutrition is safe when enteral nutrition is contraindicated.
- Providing full-dose nutrition early may lead to more metabolic and gastrointestinal complications than restrictive or trophic feeding.
- High-dose protein (>2.0 g per kilogram of body weight per day) offers no outcome benefit over standard dosing ($\leq$ 1.2 g per kilogram per day) and may be harmful in patients with acute kidney injury.
- Adverse events with enteral feeding (often called enteral feeding intolerance) are common during critical illness, and the safe delivery of nutrition requires gradual advancement, strategies for prevention of refeeding syndrome, glycemic control (glucose level, <180 mg per deciliter), and avoidance of routine gastric residual volume monitoring.
- Patient heterogeneity highlights the need for precision, appropriate use of biomarkers, and phase-specific nutrition strategies, particularly for malnourished patients and patients who survived after a stay in the intensive care unit, to preserve lean mass and improve recovery.



Metabolic Stress Response and Downstream Consequences of Critical Illness.

Critical illness activates coordinated neuroendocrine, inflammatory, and hormonal responses that promote catabolism, anabolic resistance, and cellular dysfunction, leading to organ-specific complications and adverse clinical outcomes. ICU denotes intensive care unit, and IGF-1 insulin-like growth factor 1.



Key Concept

During the early acute phase of critical illness, use restrictive-dose nutrition to support gut barrier function and avoid overfeeding during peak catabolism. As inflammation, gut dysfunction, and catabolism decrease and anabolic responsiveness increases, progressively advance the nutrition dose to meet full targets. Make up energy deficits during the recovery phase.

Evolution of Physiological Responses and Nutrition Strategy across Phases of Critical Illness.

Shown is a conceptual model of the transition from early catabolism to recovery and anabolism during critical illness, with corresponding progression from restrictive-dose to full-dose nutrition as metabolic function improves.

Major Contemporary Nutrition Trials involving Critically Ill Adults.

Topic and Trial (Year)	Population	Intervention	Comparator	Outcome	Complications
Route of nutrition delivery					
Early PN (2013) ¹⁵	1372 Patients in multiple medical-surgical ICUs	Early PN	Standard care†	No significant between-group difference in 60-day mortality (22.8% vs. 21.5%; P=0.60)	No between-group difference in infectious complications
CALORIES (2015) ¹⁶	2400 Patients in multiple medical-surgical ICUs	Early PN	Early EN	No significant between-group difference in 30-day mortality (33.1% vs. 34.2%; P=0.57)	No between-group difference in infectious complications, and more adverse events in the EN group
NUTRIREA-2 (2018) ¹⁷	2410 Patients in multiple medical-surgical ICUs	Early PN	Early EN	No significant between-group difference in 28-day mortality (35% vs. 37%; P=0.33)	No between-group difference in infectious complications, and more GI complications in the EN group
Energy dose					
EDEN (2012) ¹⁸	1000 Patients with acute lung injury at multiple medical ICUs	10 ml/hr (trophic)	25 kcal/kg/day (full dose)	No significant between-group difference in ventilator-free days or mortality	More GI complications in the 25 kcal/kg/day group
PERMIT (2015) ¹⁹	894 Patients at multiple medical-surgical ICUs	40–60% of caloric requirements (hypocaloric)‡	70–100% of caloric requirements‡	No significant between-group difference in mortality	No significant between-group difference in GI complications
REFEEDING (2015) ²⁰	339 Patients in multiple medical-surgical ICUs	20 kcal/hr for 2 days and slow ramp-up based on serum phosphate level	Standard care‡	More days alive at days 60 and 90 in the caloric-restriction group	More infections, hyperglycemic episodes, and insulin use in the standard-care group
TARGET (2019) ²¹	3957 Patients in multiple medical-surgical ICUs	1 kcal/ml formula	1.5 kcal/ml formula	No significant between-group difference in mortality	More GI complications in the 1.5 kcal/ml group
NUTRIREA-3 (2023) ²²	3044 Patients in multiple medical-surgical ICUs¶	6 kcal/kg/day‡	25 kcal/kg/day (full dose)‡	Shorter time to readiness for ICU discharge in 6 kcal/kg/day group	More severe GI complications in the 25 kcal/kg/day group
Protein dose					
EFFORT Protein (2023) ²³	1301 Patients in multiple medical-surgical ICUs	High-dose protein (≥2.2 g/kg/day)	Low-dose protein (≤1.2 g/kg/day)	No significant between-group difference in time to discharge alive at 60 days	No between-group difference in GI complications from enteral feeding
PRECISE (2024) ²⁴	935 Patients in multiple medical-surgical ICUs	High-dose protein (2.0 g/kg/day)	Standard protein (1.3 g/kg/day)	Higher health utility score with high protein than with standard protein (430 vs. 419; P=0.031)	More GI complications from enteral feeding in the high-protein group
TARGET Protein (2025) ²⁵	3397 Patients in eight medical-surgical ICUs in Australia and New Zealand	Isocaloric, protein-intense formula (100 g/liter)	Isocaloric, standard-protein formula (63 g/liter)	No significant between-group difference in days of index hospitalization and alive at day 90 (median, 62 vs. 64)	No significant between-group difference in new renal replacement therapy
Gastric residual volume monitoring					
REGANE (2010) ²⁶	329 Patients in multiple medical-surgical ICUs	Gastric residual volume threshold of 500 ml	Gastric residual volume threshold of 200 ml	No significant between-group differences in GI complications	No between-group differences in pneumonia
NUTRIREA-1 (2013) ²⁷	452 Patients in multiple medical-surgical ICUs	No gastric residual volume monitoring	Gastric residual volume threshold of 250 ml	No significant between-group difference in ventilator-associated pneumonia	More GI complications from enteral feeding in the gastric residual volume monitoring group

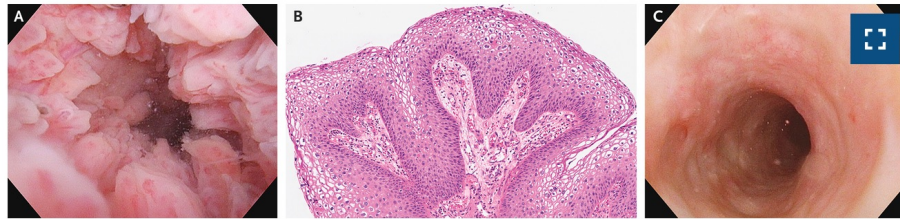
Feeding Strategies in Critically Ill Adults.

Feeding Strategy	Definition
Trophic	10–20 ml/hr of continuous feeding to nourish the intestinal mucosa ^{44,45}
Hypocaloric	<70% of caloric requirements but full dose of protein
Permissive under-feeding	40–60% of caloric and protein requirements
Full dose	70–100% of caloric and protein requirements

Conclusions

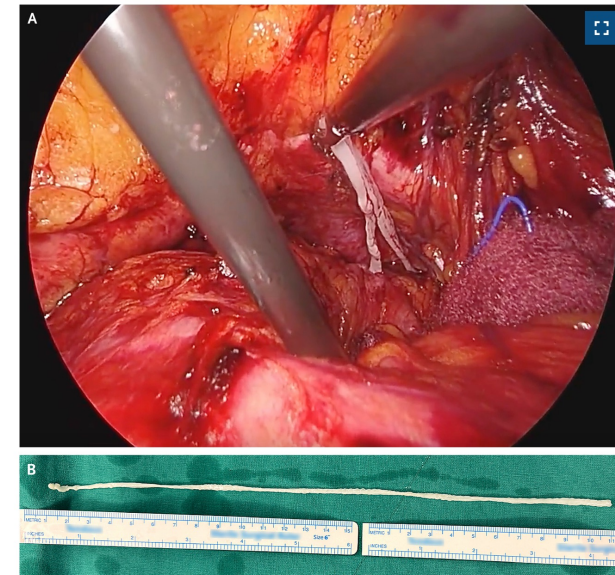
Nutrition therapy remains a cornerstone of supportive care for critically ill adults, particularly during the acute phase, when patients are unable to meet their nutritional needs through volitional intake. To support gut function, **early enteral nutrition is recommended** over early parenteral nutrition, but contemporary randomized, controlled trials suggest that early short-term parenteral nutrition is a safe option for critically ill adults who have contraindications to early enteral nutrition. Contemporary randomized, controlled trials suggest that **early full-dose nutrition during the acute phase of critical illness increases the risk of adverse events and metabolic complications** from enteral feeding, findings that support a cautious, restrictive approach to energy and protein delivery. Integration of precision nutrition — guided by biomarkers, monitoring of physiological signs, and multidisciplinary expertise — holds promise for improving outcomes and minimizing harm across the continuum of critical illness.

Condyloma Acuminata of the Urethra



A 42-year-old man presented to the urology clinic with a 2-week history of urinary frequency and weak stream. Four months before presentation, the patient had undergone stem-cell transplantation for acute lymphoblastic leukemia, which had been complicated by chronic graft-versus-host disease that had led to prolonged immunosuppressive therapy. One month before presentation, the patient had noted multiple small bumps on his penis. He was in a monogamous relationship with one sexual partner. Physical examination was notable for several small papules on the penile shaft. Urinalysis showed 9 white cells per high-power field, and a urine culture was negative. Testing for human immunodeficiency virus was also negative. Urethroscopy showed papillomatous lesions carpeting the urethral mucosa (Panel A). The penile papules were excised and identified on histopathological analysis as condyloma acuminata (genital warts), and resected urethral tissue showed papillomatous squamous proliferation with koilocytic atypia (Panel B, hematoxylin and eosin stain). A polymerase-chain-reaction assay of the excised penile-lesion specimen was positive for human papilloma virus (HPV) type 11 (the patient had not been vaccinated against HPV). A diagnosis of condyloma acuminata of the urethra was made. Treatment consisted of transurethral ablation of the lesions followed by intraurethral instillations of 5-fluorouracil and additional transurethral ablations. At follow-up 11 months after the initial diagnosis, the urethral lesions had not recurred (Panel C).

Sparganosis



A 71-year-old man was found to have a tapeworm in his peritoneal cavity during an elective repair of a right inguinal hernia. Four years earlier, a worm measuring 18 cm in length had been found incidentally and extracted during repair of a left inguinal hernia. He had not received anthelmintic agents afterward. Before the current surgery, the patient had reported no symptoms other than a painless bulge in his right groin. Preoperative laboratory testing had not shown eosinophilia. During the laparoscopic surgery, a tapeworm was removed from the space between the anterior surface of the bladder and the pubic bone (Panel A and [Video 1A](#)). The tapeworm measured 26 cm in length (Panel B) and continued to move after it had been extracted ([Video 1B](#)). Analysis by polymerase chain reaction identified the worm as *Spirometra erinaceieuropaei*. A diagnosis of sparganosis was made. Humans acquire sparganosis by consuming undercooked meat from infected snakes or frogs or by drinking water containing infected crustaceans. The larvae can migrate to various tissues and remain viable for long periods. On further history taking, the patient recalled having consumed raw snake meat during his military service 50 years earlier. Treatment with anthelmintic agents was given. At follow-up 45 days after laparoscopic surgery, the patient felt well.

VIDEO 1



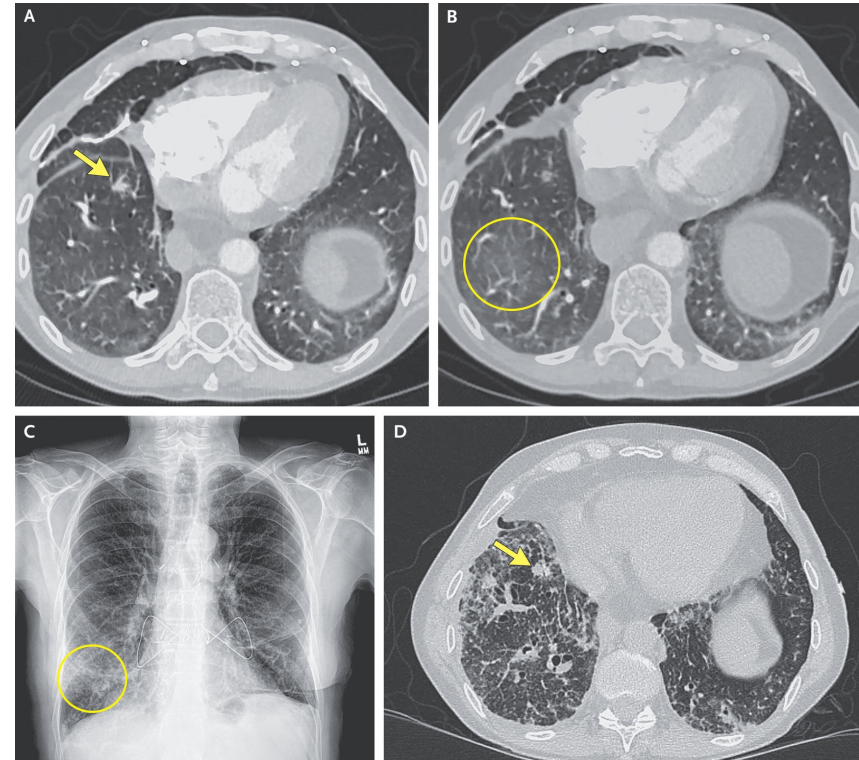
Extraction of the Tapeworm
0m 54s

Case 19-2026: A 68-Year-Old Man with Fatigue, Fever, and Hypoxemia

Fifteen months before the current presentation, the patient underwent transplantation of both lungs, with wedge resections of the right middle lobe and left upper lobe. Four months before transplantation, an interferon- γ release assay for the detection of previous exposure to *Mycobacterium tuberculosis* was negative. Donor and recipient serologic testing was performed; the donor was positive for cytomegalovirus (CMV) IgG and Epstein–Barr virus (EBV) IgG, and the recipient was negative for CMV IgG and positive for EBV IgG. At the time of lung procurement, a single granuloma in the left lower lobe was noted incidentally on chest imaging in the donor. In the recipient, histologic examination of the explanted lung tissue showed severe bullous emphysema, reactive lymph nodes, focal necrotizing granulomatous inflammation, and yeast forms. After transplantation, infection prophylaxis with trimethoprim–sulfamethoxazole, ganciclovir, and isavuconazole was started.

Two months later, and 1 month before the current presentation, the patient presented to an emergency department affiliated with this hospital because of 5 days of fever with a temperature of up to 37.8°C, fatigue, chills, chest tightness, and dyspnea with mild activity; the oxygen saturation measured at home ranged from 90 to 92% while the patient was breathing ambient air at rest and **decreased to 85% with ambulation**. In the emergency department, the oral temperature was 37.1°C, the heart rate 111 beats per minute, the respiratory rate 22 breaths per minute, and the oxygen saturation 95% while the patient was breathing ambient air. Blood electrolyte levels were normal; other laboratory test results are shown. Nucleic acid testing for SARS-CoV-2, influenza virus types A and B, and respiratory syncytial virus was negative. An electrocardiogram and a chest radiograph were reportedly normal.

Variable	Reference Range, Adults†	1 Mo before Current Evaluation, Emergency Department	2 Wk before Current Evaluation, Outpatient Clinic	On Current Evaluation, Outpatient Clinic
Tacrolimus (μg/liter)	Variable; goal of 7.0 to 9.0 in this patient in this time frame	8.7	9.1	9.5
Urea nitrogen (mg/dl)	8–25	26	29	33
Creatinine (mg/dl)	0.60–1.50	1.58	1.50	1.60
Hemoglobin (g/dl)	13.5–17.5	8.9	9.9	9.1
Hematocrit (%)	41.0–53.0	26.9	29.0	28.4
Red-cell count (per μl)	4,500,000–5,900,000	2,190,000	2,490,000	2,400,000
Mean corpuscular volume (fl)	80.0–100.0	122.5	116.5	118.3
White-cell count (per μl)	4500–11,000	4600	6000	7100
Differential count (per μl)				
Neutrophils	1800–7700	—	4270	5370
Lymphocytes	1000–4800	—	860	680
Monocytes	200–1200	—	690	820
Eosinophils	0–900	—	140	60
Immature granulocytes	0–100	—	—	150
Platelet count (per μl)	150,000–400,000	190,000	224,000	203,000
High-sensitivity troponin I (pg/liter)	0–76	12	—	—
D-Dimer (μg/ml)	<0.50	2.12	1.86	—
B-type natriuretic peptide (pg/ml)	<100	—	169	—
Cytomegalovirus DNA (IU/ml)	Negative	—	Detected but too low to be quantified	310
IgG (mg/liter)	614–1295	—	—	588



CT of the chest, performed with the administration of intravenous contrast material, showed a **nodule in the right lower lobe that measured 1 cm in diameter**, multiple new nodules in the middle and lower lobes that measured 2 to 3 mm in diameter, and an **increase in mediastinal lymphadenopathy** from 1 month earlier.

Four days later, the patient returned to the outpatient clinic to undergo bronchoscopy with transbronchial biopsy. Additional results of tests performed during the previous visit had become available: coccidioides antibody testing was negative, and the serum level of donor-derived cell-free DNA was 0.57%, near the patient's baseline level. Before the procedure, the oxygen saturation ranged from 87 to 90% while the patient was breathing ambient air at rest. Bronchoalveolar-lavage (BAL) fluid was colorless, with 5 neutrophils per microliter. Gram's staining of BAL fluid revealed rare neutrophils and no organisms; a sample was sent for culture. **Preliminary histologic examination showed patchy, mixed histiocytic and chronic inflammatory infiltrates** within alveolar walls.

Diagnostic test results were received, and management decisions were made.

Allograft Rejection

Acute cellular rejection, which can cause fever, malaise, cough, shortness of breath, and allograft dysfunction, most commonly occurs in the first year after transplantation.

Chemical Pneumonitis Due to Aspiration

This patient has risk factors for aspiration, including a hiatal hernia and gastroesophageal reflux disease.

Bacterial Infection

This patient's subacute illness and imaging findings, including a nodular infiltrate, are not suggestive of a typical acute bacterial infection such as community-acquired pneumonia.

Cytomegalovirus Infection

Lung-transplant recipients are susceptible to respiratory viral infections at any time after transplantation. However, nucleic acid testing for common respiratory viruses is a moderately sensitive diagnostic strategy and was negative in this patient.

Epstein–Barr Virus Infection

EBV-associated post-transplantation lymphoproliferative disorder (PTLD) is most likely to occur when an organ from a donor with previous EBV exposure (positive for EBV IgG) is donated to a recipient without previous EBV exposure (negative for EBV IgG).

Mycobacterial Infection

Although *M. tuberculosis* infection is not more common in lung-transplant recipients than in the general population, reactivation of latent *M. tuberculosis* infection is more common in patients with immunosuppression.

Fungal Infection

Fungal infections are an important consideration in this patient. Previous SARS-CoV-2 infection may have conferred a predisposition to superinfections or reactivation of latent infections.

Aspergillosis

Infection with aspergillus species is the most common type of fungal infection in lung-transplant recipients.

Cryptococcal Infection

Cryptococcus is an opportunistic fungus that can infect the lungs, brain, and other organs.

***Pneumocystis jirovecii* Infection**

Lung-transplant recipients are susceptible to *P. jirovecii* infection at any point after transplantation, although the risk decreases over time. This patient was receiving atovaquone prophylaxis.

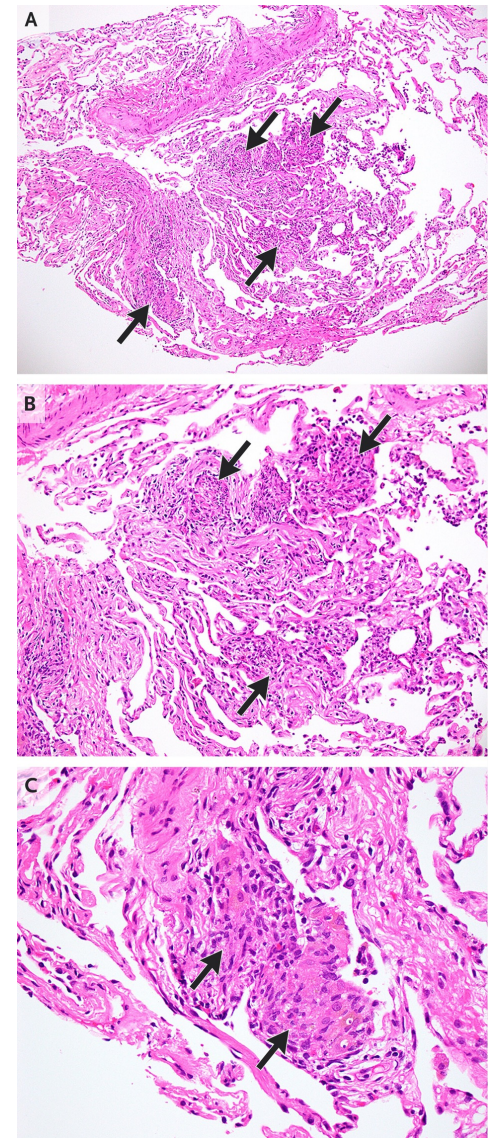
Endemic Fungal Infection

Histoplasmosis is most common in the Ohio River and Mississippi River Valleys, but it occasionally occurs in New England. This patient's gardening activity and previous exposure to birds place him at risk for exposure to *Histoplasma capsulatum*, a dimorphic fungus commonly found in soil.

Diagnostic Testing

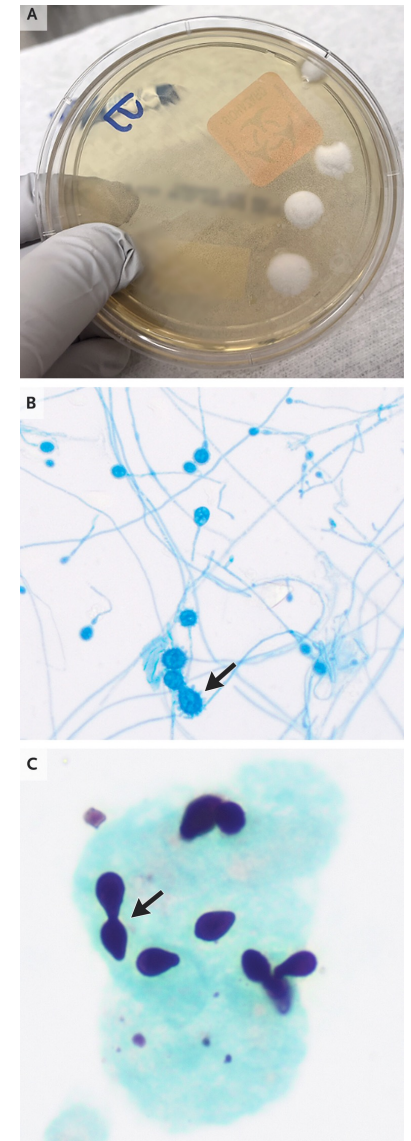
Histopathological examination of a transbronchial biopsy specimen, obtained in an assessment for allograft rejection, showed patchy, mixed histiocytic and chronic inflammatory infiltrates within the alveolar walls. These findings were suggestive of infection. Special staining for organisms, including staining for acid-fast bacilli, Grocott–methenamine silver staining, and Brown–Hopps staining, was negative. However, the absence of organisms on special staining does not rule out infection; the sensitivity of the staining is low. Aspiration was also included in the differential diagnosis but was considered to be unlikely, given the histopathological findings. There was no evidence of allograft rejection. **In this patient, serum and urinary antigen enzyme immunoassays detected histoplasma and blastomyces species.** Complement fixation and immunodiffusion antibody testing for histoplasma were negative. However, a definitive diagnosis relies on identifying the pathogen on histopathological examination, cytopathological examination, or culture.

Hematoxylin and eosin staining of a transbronchial biopsy specimen, obtained in an assessment for allograft rejection, is shown at various degrees of magnification (Panels A, B, and C). Patchy, mixed histiocytic and chronic inflammatory infiltrates are present within the alveolar walls (arrows), findings suggestive of infection. There is no evidence of allograft rejection.



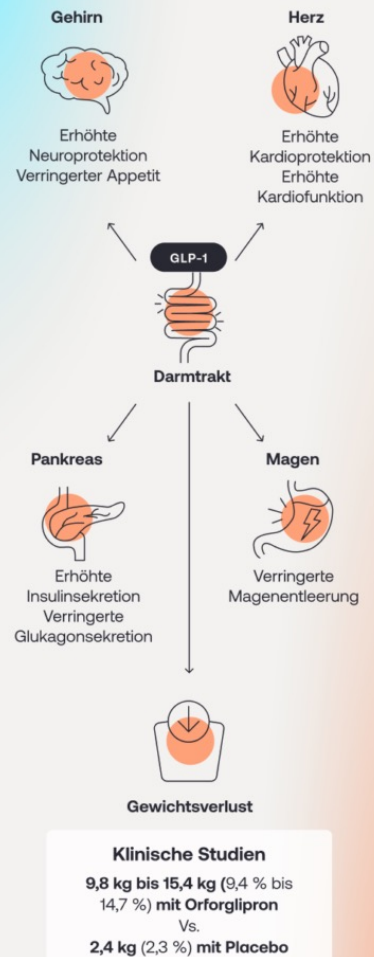
For antifungal therapy, treatment with liposomal amphotericin B was started. A course of liposomal amphotericin B was to be administered for 1 to 2 weeks, followed by prolonged oral therapy. The day after administration of the first dose, the patient had a temperature of 38.7°C, and after the second dose, he noted a marked decrease in his malaise and fatigue. The creatinine level increased to 2.57 mg per deciliter (227 μmol per liter), with the change attributable to amphotericin therapy. In a phase 2 randomized, controlled trial, outcomes with a single dose of liposomal amphotericin B were similar to those with 2 weeks of daily therapy with liposomal amphotericin B among persons with advanced human immunodeficiency virus infection and disseminated histoplasmosis. Extrapolating from these data and the potential consequences of further kidney injury, we elected to discontinue amphotericin therapy and start oral therapy. Although many physicians would prescribe itraconazole for this condition, posaconazole was chosen owing to more reliable absorption and manageable drug interactions. The patient's acute kidney injury resolved.

After 21 days of incubation at 30°C, Sabouraud dextrose agar shows the growth of white, cottony mold colonies that are consistent with *Histoplasma capsulatum* (Panel A). Lactophenol cotton blue staining shows septate hyphae with tuberculate macroconidia that are characteristic of *H. capsulatum* (Panel B, arrow). Cytologic examination with Grocott–methenamine silver staining shows numerous small, oval, narrow-based budding yeasts within macrophages (Panel C, arrow).

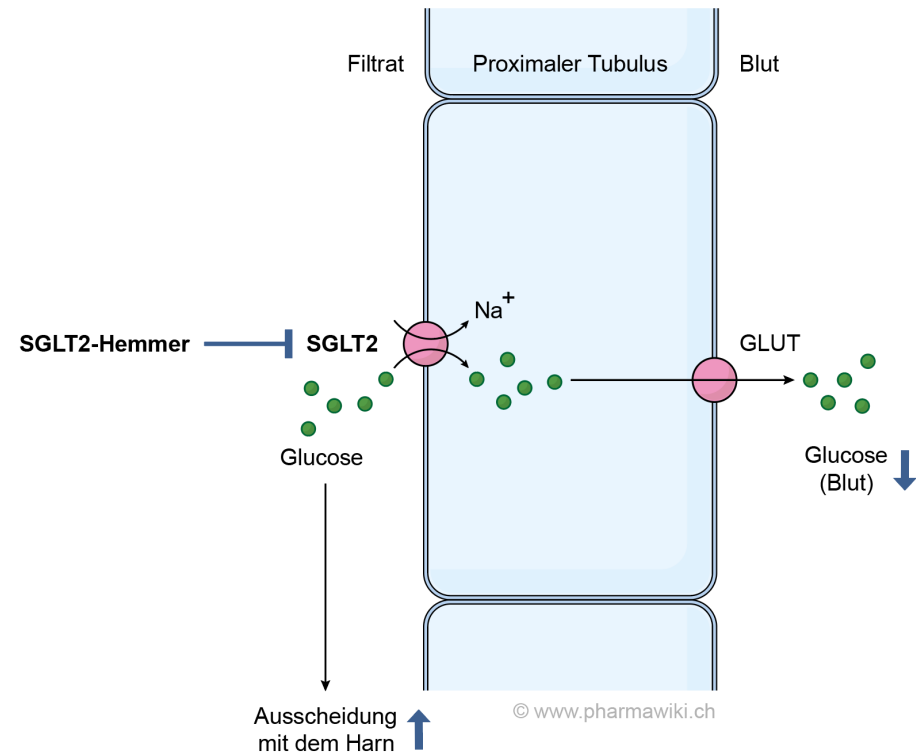


THE LANCET

Orforglipron



Dapagliflozin



Weight drives
Type-2 DM

Orforglipron compared with dapagliflozin in adults with type 2 diabetes and inadequate glycaemic control with metformin (ACHIEVE-2): a multicentre, randomised, non-inferiority, open-label, phase 3 trial

Summary

Background Type 2 diabetes is a complex metabolic disorder often requiring combination therapy for optimal glycaemic control. This study assessed the efficacy and safety of orforglipron, an oral, non-peptide GLP-1 receptor agonist, versus dapagliflozin, an oral SGLT2 inhibitor, in participants with type 2 diabetes and inadequate glycaemic control with metformin.

Methods This 40-week, phase 3, multicentre, open-label (orforglipron dose-blinded), randomised study was conducted in 73 sites across six countries. The study included adults with type 2 diabetes using metformin (≥ 1500 mg/day) with glycated haemoglobin (HbA_{1c}) concentrations between 7.0% and 10.5% (53–91 mmol/mol), stable bodyweight ($\pm 5\%$), and a BMI of 23.0 kg/m^2 or more. Participants were randomly assigned in a 1:1:1:1 ratio to receive once-daily oral orforglipron (3 mg, 12 mg, or 36 mg) or dapagliflozin 10 mg. The primary endpoint was change from baseline in HbA_{1c} at week 40, using a non-inferiority margin of 0.3% for orforglipron versus dapagliflozin; analysis was based on the treatment-regimen estimand (data obtained regardless of study intervention discontinuation or initiation of additional glucose-lowering agents). The treatment regimen estimand was the primary estimand, with the efficacy estimand considered supportive. Safety was assessed in all randomised participants who received at least one dose of study drug. This trial is registered at ClinicalTrials.gov (NCT06192108, completed).

Findings From Jan 10, 2024, to Sept 26, 2025, 1404 adults were assessed and 962 participants were randomly assigned to orforglipron 3 mg (n=240), 12 mg (n=241), or 36 mg (n=241), or dapagliflozin 10 mg (n=240). The baseline population included 474 (49%) females and had a mean age of 56·1 years (SD 11·5), HbA_{1c} of 8·14% (1·04), type 2 diabetes duration of 8·0 years (6·7), and BMI of 32·6 kg/m² (6·6). At week 40, for the treatment regimen estimand, all orforglipron doses were non-inferior to dapagliflozin in reducing HbA_{1c}. Change from baseline in mean HbA_{1c} was −1·23% (SE 0·08), −1·50% (0·08), and −1·56% (0·09) with orforglipron 3 mg, 12 mg, and 36 mg, respectively, versus −0·81% (0·07) with dapagliflozin 10 mg; estimated treatment difference versus dapagliflozin was −0·42% (95% CI −0·62 to −0·23), −0·70% (−0·90 to −0·49), and −0·75% (−0·96 to −0·55) with orforglipron 3 mg, 12 mg, and 36 mg, respectively (all p<0·0001). The most frequent adverse events associated with orforglipron were mild-to-moderate gastrointestinal events, observed in 112 (47%) of 240 participants receiving orforglipron 3 mg, 112 (46%) of 241 receiving 12 mg, and 130 (54%) of 241 receiving 36 mg, versus 29 (12%) of 240 receiving dapagliflozin. More study intervention discontinuations were observed with orforglipron 3 mg (35 [15%] of 240), 12 mg (44 [18%] of 241), and 36 mg (47 [20%] of 241) than with dapagliflozin (14 [6%] of 240). No severe episode of hypoglycaemia was reported.

Interpretation Orforglipron demonstrated superior glycaemic control compared with dapagliflozin, with a tolerability profile consistent with the GLP-1 receptor agonist class, including increased rates of discontinuation due to adverse events, positioning it as a potential effective oral treatment option for type 2 diabetes.

Funding Eli Lilly and Company.

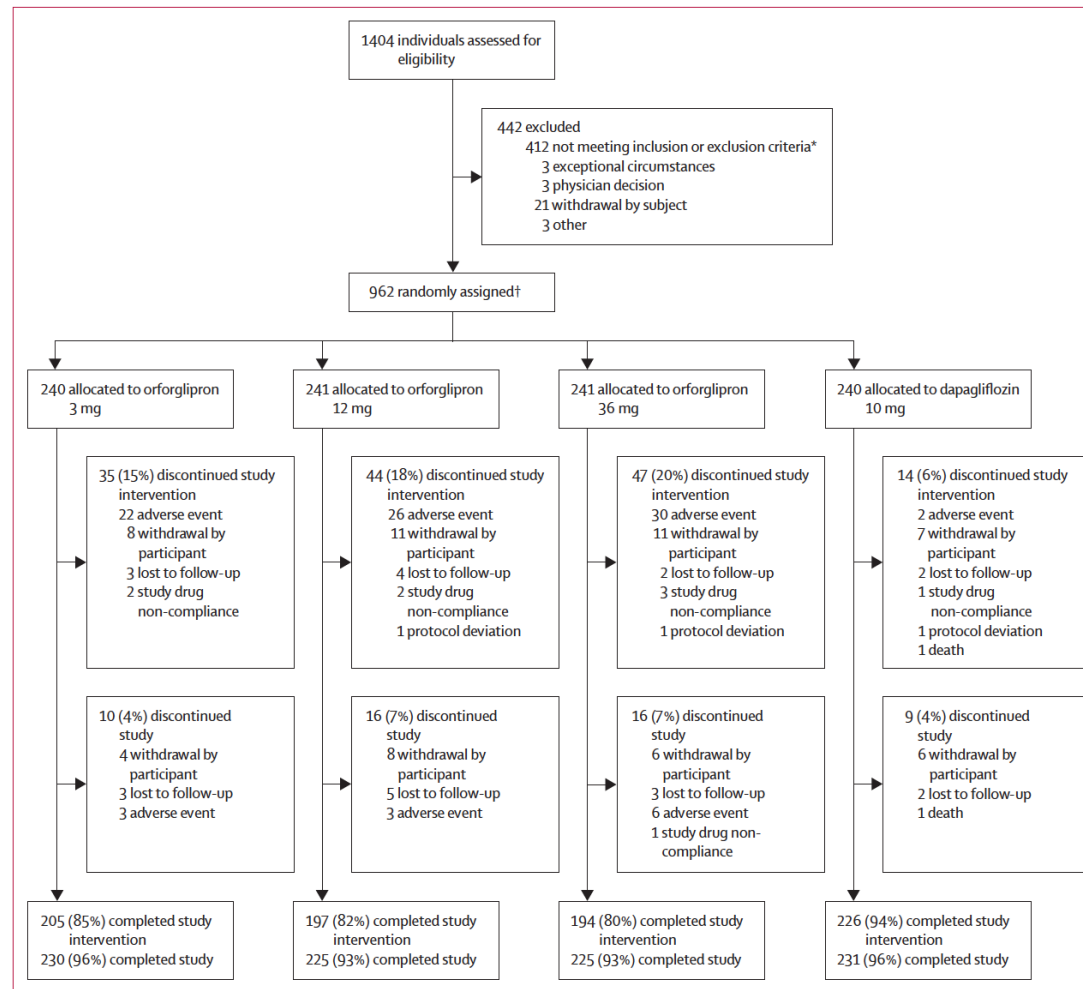
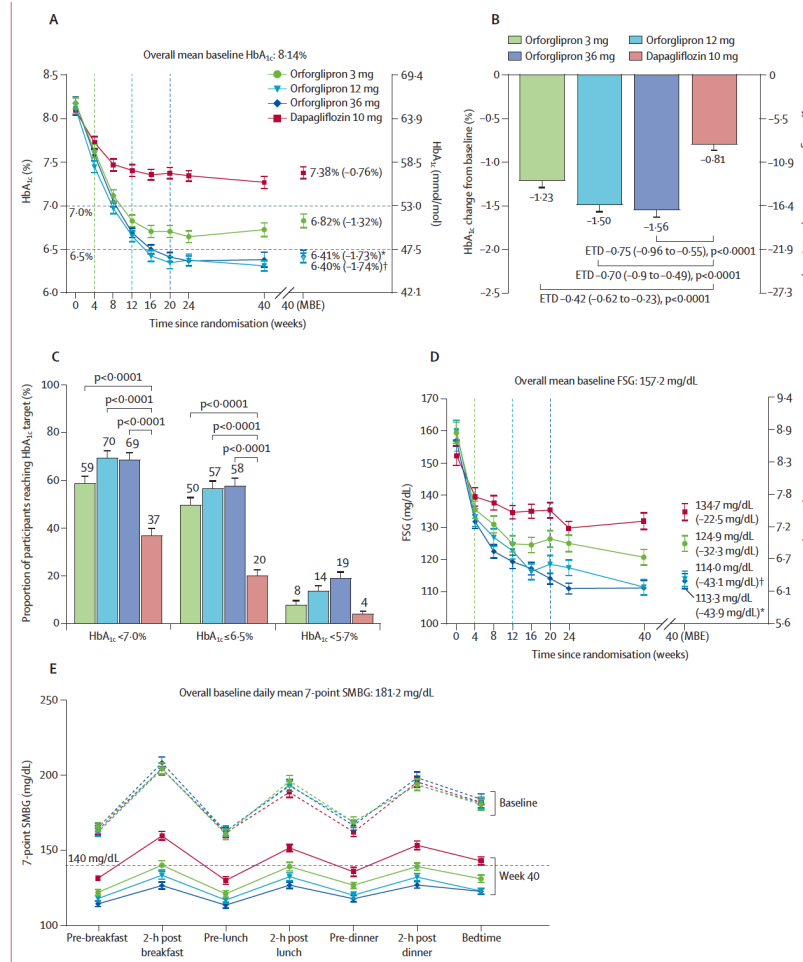


Figure 1: Trial profile

Study completion is defined as completing both the 40-week treatment period and the safety follow-up period. If participants discontinue the study during the treatment period, they also discontinue the study intervention, either earlier, or at the same time. Reason for study discontinuation is considered the earliest discontinuation reason from either treatment period or safety follow-up period. *For full details on the inclusion criteria and the complete list refer to the appendix (pp 10-13). †All randomised participants received study treatment.

	Orforglipron 3 mg (n=240)	Orforglipron 12 mg (n=241)	Orforglipron 36 mg (n=241)	Dapagliflozin 10 mg (n=240)	Overall population (n=962)
Demographic variables					
Age, years	55.1 (11.8)	55.9 (11.6)	56.6 (11.5)	56.6 (11.1)	56.1 (11.5)
Sex					
Female	117 (49%)	121 (50%)	123 (51%)	113 (47%)	474 (49%)
Male	123 (51%)	120 (50%)	118 (49%)	127 (53%)	488 (51%)
Race*					
White	119 (50%)	125 (52%)	131 (54%)	125 (52%)	500 (52%)
American Indian or Alaska Native	67 (28%)	62 (26%)	53 (22%)	61 (25%)	243 (25%)
Asian	43 (18%)	42 (17%)	44 (18%)	42 (18%)	171 (18%)
Multiple	5 (2%)	5 (2%)	11 (5%)	6 (3%)	27 (3%)
Black or African American	6 (3%)	6 (2%)	2 (1%)	6 (3%)	20 (2%)
Ethnicity					
Not Hispanic or Latino	124 (52%)	125 (52%)	122 (51%)	124 (52%)	495 (51%)
Hispanic or Latino	114 (48%)	114 (47%)	116 (48%)	114 (48%)	458 (48%)
Not reported	2 (1%)	2 (1%)	3 (1%)	2 (1%)	9 (1%)
Country					
Mexico	99 (41%)	100 (41%)	100 (41%)	100 (42%)	399 (41%)
Poland	36 (15%)	36 (15%)	36 (15%)	35 (15%)	143 (15%)
USA	35 (15%)	35 (15%)	36 (15%)	35 (15%)	141 (15%)
Germany	30 (13%)	29 (12%)	29 (12%)	29 (12%)	117 (12%)
China	25 (10%)	26 (11%)	25 (10%)	26 (11%)	102 (11%)
Taiwan	15 (6%)	15 (6%)	15 (6%)	15 (6%)	60 (6%)
Clinical variables					
HbA _{1c} , %	8.17 (1.08)	8.11 (1.05)	8.18 (1.08)	8.09 (0.98)	8.14 (1.04)
HbA _{1c} , mmol/mol	65.8 (11.8)	65.2 (11.5)	65.9 (11.8)	65.0 (10.7)	65.5 (11.4)
HbA _{1c} category					
HbA _{1c} ≤8.0%	126 (53%)	129 (54%)	128 (53%)	130 (54%)	513 (53%)
HbA _{1c} >8.0%	114 (48%)	112 (46%)	113 (47%)	110 (46%)	449 (47%)
Fasting serum glucose, mg/dL	159.4 (52.5)	160.1 (51.1)	157.0 (49.5)	152.3 (49.4)	157.2 (50.6)
Fasting serum glucose, mmol/L	8.9 (2.9)	8.9 (2.8)	8.7 (2.8)	8.5 (2.7)	8.7 (2.8)
Bodyweight, kg	90.1 (20.4)	92.1 (23.6)	88.1 (22.0)	89.4 (21.1)	89.9 (21.8)
BMI, kg/m ²	32.4 (6.5)	33.2 (7.0)	32.2 (6.6)	32.4 (6.5)	32.6 (6.6)
Waist circumference, cm	107.0 (14.8)	108.0 (15.7)	106.3 (14.7)	107.2 (14.8)	107.1 (15.0)
Duration of type 2 diabetes, years	7.4 (6.4)	7.9 (6.6)	8.1 (7.1)	8.5 (6.7)	8.0 (6.7)
Previous use of GLP-1 receptor agonist (yes)	15 (6%)	12 (5%)	12 (5%)	15 (6%)	54 (6%)
Blood pressure, mm Hg					
Systolic	127.6 (11.4)	128.1 (14.2)	127.7 (12.8)	128.3 (12.4)	127.9 (12.7)
Diastolic	79.5 (8.2)	80.2 (8.3)	79.5 (9.2)	80.0 (8.0)	79.8 (8.4)
Pulse rate, beats per min	74.1 (10.2)	75.2 (9.7)	74.7 (10.2)	73.8 (10.0)	74.5 (10.0)
eGFR, mL/min per 1.73 m ²	87.8 (20.4)	87.5 (20.1)	87.8 (18.8)	85.8 (20.7)	87.2 (20.0)
Triglycerides, mg/dL	167.9 (106.4)	184.9 (221.3)	174.0 (131.5)	162.7 (78.7)	172.4 (144.8)
Non-HDL cholesterol, mg/dL	126.3 (44.1)	131.6 (43.1)	133.7 (52.7)	128.7 (41.6)	130.1 (45.6)
Data are n (%) or mean (SD). eGFR=estimated glomerular filtration rate. HbA _{1c} =glycated haemoglobin. *One participant missing for race parameter, n=240 for orforglipron 12 mg.					
Table 1: Baseline demographics and clinical variables of all randomly assigned participants					

HbA1C



FBS

Blood sugar

Figure 2: HbA_{1c}, proportion of participants reaching HbA_{1c} targets, FSG, and 7-point SMBG profiles
 (A) Over time curve data are observed mean HbA_{1c} for the efficacy estimand; MBE at week 40 is actual value (change from baseline) for the efficacy estimand.
 (B) Change from baseline in HbA_{1c} and ETD with p values versus dapagliflozin 10 mg at week 40 from ANCOVA for the treatment regimen estimand. (C) Proportion of participants achieving HbA_{1c} targets of <7.0%, ≤6.5%, and <5.7% and p values versus dapagliflozin 10 mg at week 40 from logistic regression analysis for the treatment regimen estimand. (D) Over time curve data are observed mean FSG for the efficacy estimand; MBE at week 40 is absolute value (change from baseline) for the efficacy estimand. (E) MBE mean 7-point SMBG profiles at baseline (dotted lines) and week 40 (full lines) for the efficacy estimand. In every panel, error bars denote SE. In panels A and D, vertical dotted lines denote the end of dose escalation periods for each orforglipron treatment group. In panels B and C, only p values tested for multiplicity (family-wise type-1 error) are shown. ETD=estimated treatment difference. FSG=fasting serum glucose. HbA_{1c}=glycated haemoglobin. MBE=model-based estimate. SMBG=self-monitored blood glucose. *Denotes orforglipron 36 mg group where lines overlap. †Denotes orforglipron 12 mg group where lines overlap.

Weight loss

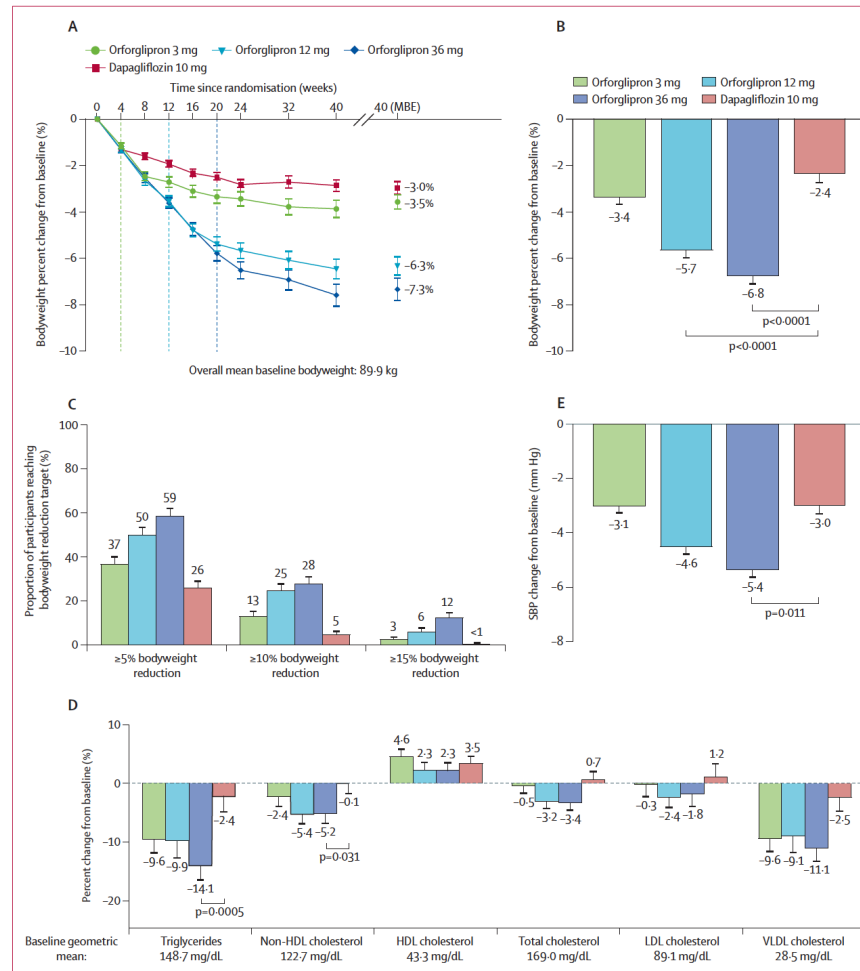


Figure 3: Bodyweight change, proportion of participants reaching bodyweight reduction targets, lipid profile, and SBP
 (A) Over time curve data are observed percent change from baseline in bodyweight for the efficacy estimand, MBE at week 40 is actual value (change from baseline) for the efficacy estimand. (B) Percent change from baseline in bodyweight and p values versus dapagliflozin 10 mg at week 40 from ANCOVA for the treatment regimen estimand. (C) Proportion of participants reaching bodyweight reduction targets of $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ at week 40 from logistic regression analysis for the treatment regimen estimand. (D) Percent change from baseline in lipids and p values versus dapagliflozin 10 mg at week 40 from ANCOVA for the treatment regimen estimand. (E) Change from baseline in SBP and p values versus dapagliflozin 10 mg at week 40 from ANCOVA for the treatment regimen estimand. In every panel, error bars denote SE. In panel A, vertical dotted lines denote the end of dose escalation periods for each orforglipron treatment group. In panels B, D, and E, only p values tested for multiplicity (family-wise type-1 error) are shown. MBE=model-based estimate. SBP=systolic blood pressure.

	Orforglipron 3 mg (n=240)	Orforglipron 12 mg (n=241)	Orforglipron 36 mg (n=241)	Dapagliflozin 10 mg (n=240)
Participants with ≥1 TEAE	165 (69%)	168 (70%)	170 (71%)	129 (54%)
Serious adverse events	8 (3%)	14 (6%)	9 (4%)	11 (5%)
Adverse events leading to death*	0	0	0	1 (<1%)
Adverse events leading to study discontinuation*	3 (1%)	3 (1%)	6 (2%)	1 (<1%)
Adverse events leading to intervention discontinuation*	22 (9%)	26 (11%)	30 (12%)	3 (1%)
Gastrointestinal adverse events	14 (6%)	18 (7%)	20 (8%)	1 (<1%)
Vomiting	2 (1%)	5 (2%)	7 (3%)	0
Nausea	2 (1%)	3 (1%)	4 (2%)	0
Diarrhoea	3 (1%)	3 (1%)	0	0
Abdominal pain	1 (<1%)	1 (<1%)	2 (1%)	0
Dyspepsia	0	2 (1%)	2 (1%)	0
Other gastrointestinal adverse events	6 (3%)	4 (2%)	5 (2%)	1 (<1%)
Non-gastrointestinal adverse events	8 (3%)	8 (3%)	10 (4%)	2 (1%)
Adverse events occurring in ≥5% of participants in any treatment group				
Nausea	47 (20%)	41 (17%)	53 (22%)	3 (1%)
Diarrhoea	44 (18%)	40 (17%)	48 (20%)	11 (5%)
Vomiting	19 (8%)	20 (8%)	29 (12%)	4 (2%)
Constipation	19 (8%)	20 (8%)	25 (10%)	2 (1%)
Dyspepsia	15 (6%)	12 (5%)	25 (10%)	2 (1%)
Decreased appetite	12 (5%)	8 (3%)	20 (8%)	0
Abdominal distension	12 (5%)	12 (5%)	19 (8%)	3 (1%)
Eructation	13 (5%)	10 (4%)	12 (5%)	0
Gastro-oesophageal reflux disease	7 (3%)	6 (2%)	13 (5%)	1 (<1%)
Lipase increased	12 (5%)	14 (6%)	13 (5%)	7 (3%)
Nasopharyngitis	14 (6%)	13 (5%)	16 (7%)	10 (4%)
Diabetic retinopathy	5 (2%)	8 (3%)	8 (3%)	17 (7%)
Vulvovaginal mycotic infection†	0	0	1 (1%)	6 (5%)
Hyperglycaemia	14 (6%)	6 (2%)	3 (1%)	15 (6%)
All gastrointestinal adverse events	112 (47%)	112 (46%)	130 (54%)	29 (12%)
Other adverse events of interest				
Hypoglycaemia (blood glucose <54 mg/dL)	1 (<1%)	3 (1%)	3 (1%)	3 (1%)
Severe hypoglycaemia‡	0	0	0	0
Initiation of rescue therapy for severe persistent hyperglycaemia	9 (4%)	4 (2%)	2 (1%)	13 (5%)
Diabetic retinopathy complications, diabetic macular oedema, and related complications	7 (3%)	11 (5%)	10 (4%)	18 (8%)
Adjudication-confirmed pancreatitis§	1 (<1%)	1 (<1%)	0	0
Treatment-emergent gallbladder and biliary tract disorders§	3 (1%)	1 (<1%)	1 (<1%)	2 (1%)
Cholelithiasis	2 (1%)	1 (<1%)	0	1 (<1%)
Adjudication-confirmed MACE¶	1 (<1%)	1 (<1%)	2 (1%)	2 (1%)
Urinary tract infection	7 (3%)	3 (1%)	5 (2%)	11 (5%)
Data are n (%) of participants for the safety datapoints set. Participants can be counted in more than one category. MACE=major adverse cardiac event. TEAE=treatment-emergent adverse event. *Deaths are also included as serious adverse events and discontinuations due to adverse events. †Denominator adjusted because this is a sex-specific event for females: n=117 (orforglipron 3 mg); n=121 (orforglipron 12 mg); n=123 (orforglipron 36 mg); n=113 (dapagliflozin 10 mg). ‡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 glucose-lowering agent. §One participant in the orforglipron 3 mg group reported gallstone pancreatitis, which was included in both adverse event categories of "adjudication-confirmed pancreatitis" and "treatment-emergent gallbladder and biliary tract disorders". ¶IMACE (confirmed by clinical endpoint committee) includes: deaths due to cardiovascular cause, myocardial infarction, hospitalisation for unstable angina or heart failure, coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention), and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischaemic attack.				
Table 2: Adverse events and safety during the study period				

Added value of this study

ACHIEVE-2 is the first phase 3, randomised study to directly compare orforglipron with an SGLT2 inhibitor, dapagliflozin, in adults with type 2 diabetes inadequately controlled by metformin. In this study, once-daily oral administration of orforglipron without food or water restriction resulted in non-inferior, and superior improvements in glycaemic control compared with dapagliflozin, without increasing the risk of clinically significant hypoglycaemia. Compared with dapagliflozin, orforglipron 12 mg and 36 mg demonstrated greater bodyweight reduction after 40 weeks, and orforglipron 36 mg demonstrated improvement in cardiometabolic risk factors, including triglycerides, non-HDL cholesterol, and systolic blood pressure. Orforglipron also demonstrated a safety profile consistent with the GLP-1 receptor agonist class, mainly characterised by mild-to-moderate and generally transient gastrointestinal adverse events, as well as increased rates of discontinuation due to adverse events. The head-to-head results from the ACHIEVE-2 study provide direct comparative evidence that orforglipron is non-inferior and superior to dapagliflozin in the predefined endpoints.

Implications of all the available evidence

The improvements in glycaemic control, bodyweight reduction, and improvements in selected cardiometabolic risk factors observed with orforglipron compared with dapagliflozin in the present ACHIEVE-2 study, combined with findings from ACHIEVE-1 and ACHIEVE-3, suggest that orforglipron constitutes an important therapeutic option for people living with type 2 diabetes. Findings could inform decision making for clinicians selecting second-line therapy to combine with metformin for the treatment of type 2 diabetes.

Staphylococcus aureus ist ein weit verbreitetes, kugelförmiges Bakterium, das bei etwa 20 bis 30 % aller gesunden Menschen völlig harmlos auf der Haut und den Schleimhäuten (besonders in der Nase) vorkommt. Wenn es jedoch über Wunden in den Körper gelangt oder das Immunsystem geschwächt ist, kann es eine Vielzahl von Infektionen auslösen.

Hautinfektionen: Dazu gehören kleine, schmerzhaft Pickel an den Haarwurzeln (Follikulitis), eitrige Bläschen (Impetigo) sowie größere Eiteransammlungen unter der Haut (Abszesse oder Furunkel).

Lebensmittelvergiftung: Bestimmte Stämme bilden Giftstoffe (Toxine) in Nahrungsmitteln, die nach dem Verzehr zu heftigem Erbrechen und Durchfall führen.

Innere Infektionen: Dringt der Keim tiefer in den Körper vor, kann er Organe befallen und Lungenentzündungen, Knochenentzündungen (Osteomyelitis) oder Herzentzündungen auslösen.

Sepsis und Schocksyndrom: Gelangt das Bakterium in die Blutbahn, droht eine lebensgefährliche Blutvergiftung (Sepsis) oder ein Toxisches Schocksyndrom (TSS) mit Organversagen



"Penicillin-empfindlich" (**PSSA**) und "**MSSA**" sind **nicht exakt dasselbe**, auch wenn beide auf Methicillin und ähnliche Antibiotika ansprechen. Die Unterscheidung liegt im Detail der Resistenz:

- MSSA (Methicillin-sensibler Staphylococcus aureus)**: Dieser Stamm ist empfindlich gegenüber Methicillin (und damit auch gegen Penicilline, sofern diese nicht durch spezielle Enzyme der Bakterien zerstört werden).

- PSSA (Penicillin-susceptible Staphylococcus aureus)**: Das sind MSSA-Stämme, die *zusätzlich* auch gegen das klassische Penicillin G empfindlich sind.

Der feine Unterschied:

Die meisten Staphylokokken bilden ein Enzym (Penicillinase), das normales Penicillin zerstört. Sie sind daher resistent gegen Penicillin, bleiben aber oft empfindlich gegenüber Methicillin (das ist dann der klassische **MSSA**). Wenn ein Stamm jedoch sowohl gegen Methicillin *als auch* gegen Penicillin empfindlich ist, nennt man ihn PSSA.

PSSA and MSSA are not the same.

For PSSA Benzyl-PCN is OK

Benzylpenicillin versus flucloxacillin or cloxacillin for the treatment of penicillin-susceptible *Staphylococcus aureus* bacteraemia (SNAP): an international, multicentre, open-label, non-inferiority randomised controlled trial

Summary

Background Previously considered rare, penicillin-susceptible *Staphylococcus aureus* (PSSA) bacteraemia has re-emerged worldwide. Although benzylpenicillin might offer advantages in terms of pharmacokinetic and adverse effect profiles, anti-staphylococcal penicillins are recommended for serious infections because of concern over undetected penicillin resistance. We aimed to compare benzylpenicillin with anti-staphylococcal penicillins (cloxacillin or flucloxacillin) for the treatment of PSSA bacteraemia in adults.

Methods This investigator-initiated, international, multicentre, open-label, non-inferiority, randomised controlled trial was conducted within the PSSA silo of the backbone domain of the ongoing *S aureus* Network Adaptive Platform (SNAP) trial. We enrolled patients of all ages who were admitted with *S aureus* bacteraemia at 67 hospitals across Australia, New Zealand, Canada, Israel, the Netherlands, the UK, Singapore, and South Africa. Herein, we report results for adult patients (aged ≥ 18 years). Participants were randomly allocated 1:1 to receive either benzylpenicillin, or flucloxacillin or cloxacillin. Trial staff, staff caring for participants, and participants were aware of the treatment allocated and received. Cloxacillin was used only where flucloxacillin was not available (ie, Canada, Israel, Singapore, and South Africa). Recommended standard dosing for benzylpenicillin was 1.8 g intravenously once every 4 h or 2.4 g once every 6 h; for flucloxacillin 2.0 g intravenously once every 6 h; and for cloxacillin 2.0 g intravenously once every 4 h. The primary outcome was all-cause mortality 90 days after platform entry, assessed in the intention-to-treat population, including all patients with available data. The primary outcome was analysed by use of a hierarchical Bayesian logistic regression model, with non-inferiority of benzylpenicillin defined as an adjusted odds ratio (OR) of less than 1.20. Analyses occurred after every 500 participants reached 90-day follow-up. The SNAP trial is registered with ClinicalTrials.gov (NCT05137119) and is ongoing.

Findings Following the fourth interim analysis, the data and safety monitoring committee recommended ceasing recruitment before prespecified stopping thresholds were reached because of increased acute kidney injury (AKI) in participants receiving flucloxacillin or cloxacillin, and the PSSA silo was closed for recruitment on Aug 7, 2024. Between Feb 18, 2022, and June 21, 2024, of 493 adults with PSSA bacteraemia, 125 were randomly assigned to the flucloxacillin or cloxacillin group and 156 to the benzylpenicillin group. The median age was 67 years (IQR 56–77), 87 (31%) were female, and 194 (69%) were male. 21 (14%) of 152 in the benzylpenicillin group and 26 (22%) of 121 in the flucloxacillin or cloxacillin group met the primary outcome of death at 90 days (adjusted OR 0·67, 95% credible interval [CrI] 0·35–1·28), with a posterior probability of benzylpenicillin non-inferiority of 96·1% and of benzylpenicillin superiority of 88·9%. AKI occurred in 17 (11%) of 153 patients in the benzylpenicillin group and 27 (22%) of 124 patients in the flucloxacillin or cloxacillin group (adjusted OR 0·50, 95% CrI 0·26–0·94), corresponding to a posterior probability of non-inferiority of benzylpenicillin of 99·8% and superiority of benzylpenicillin of 98·4%. Seven total serious adverse reactions were reported from six (4%) of 156 participants in the benzylpenicillin group and ten were reported from nine (7%) of 125 participants in the flucloxacillin or cloxacillin group.

Interpretation Although the prespecified non-inferiority criterion for benzylpenicillin was not met, the probability of benzylpenicillin being non-inferior for mortality, along with a reduction in risk of AKI, indicates that benzylpenicillin should be preferred over flucloxacillin or cloxacillin for treatment of PSSA bacteraemia in adults.

Funding National Health and Medical Research Council, Medical Research Future Fund, Canadian Institutes of Health Research, Accelerating Clinical Trials Consortium, UMC Utrecht, ZonMW Good Use of Medicines programme, Health Research Council of New Zealand, Starship Foundation, National Healthcare Group Fund, National Medical Research Council, National Institute for Health and Care Research, Medical Research Council, and Paterson Family Foundation.

Both cefazolin and benzylpenicillin (penicillin G) are highly affordable, generic intravenous antibiotics, with cefazolin typically ranging from €4 to €8 per gram-equivalent and benzylpenicillin varying between €5 and €15 per vial. Looks like cefazolin is cheapest.

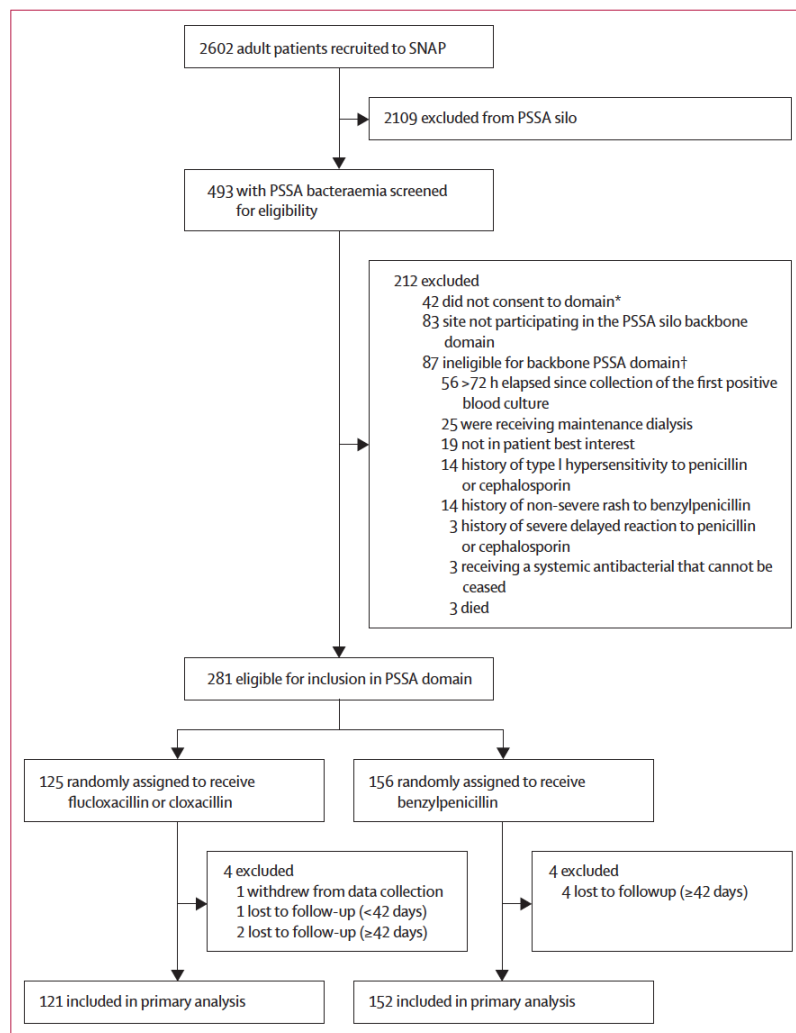


Figure: Trial profile

PSSA=penicillin-susceptible *Staphylococcus aureus*. SNAP=Staphylococcus aureus Network Adaptive Platform.

*Includes consent not sought. †Participants could meet more than one exclusion criteria.

	Benzylpenicillin (n=156)	Flucloxacillin or cloxacillin (n=125)
Demographics		
Age, years	65.5 (55.8-75.2)	69.0 (57.0-79.0)
Sex		
Female	46 (29%)	41 (33%)
Male	110 (71%)	84 (67%)
Weight, kg	80.0 (70.0-97.0)	82.0 (70.0-95.0)
Comorbidities		
Diabetes	48 (31%)	43 (34%)
Chronic kidney disease*	20 (13%)	14 (11%)
Cirrhosis	7 (4%)	8 (6%)
Cancer requiring any surgical or medical therapy within 12 months†	16 (10%)	15 (12%)
Dementia	10 (6%)	6 (5%)
Iatrogenic immunosuppression‡	19 (12%)	16 (13%)
Implanted intravascular prosthesis or endovascular device§	15 (10%)	16 (13%)
Previous infective endocarditis	4 (3%)	2 (2%)
Underlying cardiac abnormality predisposing to endocarditis¶	13 (8%)	5 (4%)
Injection drug use within 6 months	7 (4%)	5 (4%)
Limitations to care	21 (13%)	19 (15%)
Prognostic factors		
Time from index blood culture collection to index blood culture positivity, hours	16.4 (12.4-21.2)	14.9 (12.0-18.1)
Time from index blood culture to platform entry, hours	54.4 (44.4-65.1)	49.0 (39.9-64.9)
Time from index blood culture to domain entry, hours	63.4 (54.3-68.2)	63.7 (51.5-68.1)
Admitted to intensive care unit at time of recruitment	23 (15%)	11 (9%)
Median Pitt Bacteraemia Score	0 (0-1)	0 (0-1)
Median C-reactive protein, mg/L	184 (125.8-268.5)	194.0 (126.0-276.0)
Receipt of antibiotics between index blood culture and platform entry	155 (99%)	124 (99%)
Clinical quality indicators		
Review by infectious disease specialist**	153 (98%)	122 (98%)

Data are n (%) or median (IQR). *Defined as estimated glomerular filtration rate below 50 mL/min per 1.72 m². †Excluding non-melanoma skin cancers. ‡Defined as patients who, within past 3 months, have received any of the following: prednisone 0.5 mg/kg per day or more (or equivalent) for more than 14 days; ciclosporin, tacrolimus, or sirolimus; azathioprine, leflunomide, or mycophenolate; cyclophosphamide or methotrexate; monoclonal antibodies such as infliximab; cancer chemotherapy; bone marrow transplantation; other immunosuppressive agents equal to those mentioned. §Not including central lines, whether temporary or tunnelled. ¶Excluding implanted intravascular prosthesis or endovascular device. ||Defined as active orders or advance care directives limiting resuscitation and intensive care admission. **During index hospitalisation, which excludes time when transferred to another acute care facility where further data may not be available.

Table 1: Baseline characteristics of adult patients

	Benzylpenicillin (n=156)	Flucloxacillin or cloxacillin (n=125)
Osteoarticular (including epidural abscess)	49 (31%)	36 (29%)
Septic arthritis and extra-axial osteomyelitis	27 (17%)	19 (15%)
Vertebral osteomyelitis or septic discitis	10 (6%)	4 (3%)
Epidural abscess	14 (9%)	8 (6%)
Orthopaedic hardware- associated bone and joint infection	4 (3%)	6 (5%)
Skin and soft tissue	45 (29%)	30 (24%)
Isolated skin and soft tissue	32 (21%)	20 (16%)
Primary bacteraemia†	20 (13%)	19 (15%)
Intravascular catheter associated	17 (11%)	20 (16%)
Isolated intravascular catheter infection	16 (10%)	17 (14%)
Endocarditis	8 (5%)	15 (12%)
Left-sided native valve	7 (4%)	10 (8%)
Right-sided native valve	2 (1%)	6 (5%)
Prosthetic valve	0	1 (1%)
Cardiac or other implantable non-orthopaedic device	14 (9%)	8 (6%)
Other deep focus	7 (4%)	3 (2%)
Pleuropulmonary	4 (3%)	4 (3%)
Genitourinary	4 (3%)	4 (3%)
Central nervous system	2 (1%)	1 (1%)

Data are n (%). *More than one focus could be included for each patient. †Primary bacteraemia refers to cases where no other focus of infection is clinically apparent.

Table 2: Focus of infection*

	Benzylpenicillin (n=156)	Flucloxacillin or cloxacillin (n=125)	Median-adjusted odds ratio (95% CrI)	Posterior probability of benzylpenicillin non- inferiority*†	Posterior probability of benzylpenicillin superiority†‡
Primary outcome: 90-day all-cause mortality					
Primary analysis population	21/152 (14%)	26/121 (21%)	0.67 (0.35–1.28)	96.1%	88.9%
Protocol-adherent population	9/122 (7%)	19/103 (18%)	0.43 (0.19–0.93)	99.6%	98.4%
Secondary outcomes					
Acute kidney injury§¶	17/153 (11%)	27/124 (22%)	0.50 (0.26–0.94)	99.8%	98.4%
14-day mortality	10/156 (6%)	8/125 (6%)	1.14 (0.47–2.76)	NE	NE
28-day mortality	13/156 (8%)	16/124 (13%)	0.77 (0.36–1.62)	NE	NE
42-day mortality	18/156 (12%)	17/123 (14%)	1.00 (0.49–2.00)	NE	NE
Change of antibiotic due to perceived inefficacy	11/156 (7%)	1/125 (1%)	5.82 (1.74–30.28)	NE	NE
Microbiological treatment failure after day 14	6/141 (4%)	3/106 (3%)	1.30 (0.42–4.00)	NE	NE
Diagnosis of new foci of infection after day 14	7/143 (5%)	6/113 (5%)	0.90 (0.33–2.40)	NE	NE
Treatment failure by day 90§	32/148 (22%)	32/113 (28%)	0.75 (0.42–1.33)	99.9%	NE
Change of antibiotic due to any adverse event§	8/156 (5%)	10/125 (8%)	0.79 (0.31–1.99)	NE	NE
Any serious adverse reaction related to study drug§	6/156 (4%)	9/125 (7%)	0.79 (0.29–2.02)	NE	NE
New renal replacement therapy within 90 days§	3/156 (2%)	5/125 (4%)	0.57 (0.17–1.79)	NE	NE
Ongoing renal replacement therapy at 90 days§	0/155 (0%)	0/123 (0%)	0.59 (0.07–3.81)	NE	NE
Hepatotoxicity within 14 days§**	18/145 (12%)	17/107 (16%)	0.76 (0.37–1.50)	NE	NE
<i>Clostridioides difficile</i> infection§	0/156 (0%)	1/123 (1%)	0.39 (0.05–2.07)	NE	NE
Intravenous catheter complication requiring removal§	7/156 (4%)	6/125 (5%)	0.84 (0.31–2.18)	NE	NE
Prespecified subgroup analysis: 90-day mortality					
No endocarditis subgroup	20/143 (14%)	23/106 (22%)	0.69 (0.34–1.33)	NE	NE
Endocarditis subgroup	1/8 (13%)	3/15 (20%)	0.99 (0.17–5.40)	NE	NE
Post-hoc analysis assuming all those with missing primary outcome data are either alive or dead					
All missing assumed to be dead at 90 days	25/156 (16%)	30/125 (24%)	0.68 (0.3, 1.22)	NE	NE
All missing assumed to be alive at 90 days	21/156 (13%)	26/125 (21%)	0.70 (0.37–1.32)	NE	NE

Data are n/N (%) unless otherwise specified. AKI=acute kidney injury. CrI=credible interval. NE=not estimated. *Non-inferiority was defined as an adjusted odds ratio of less than 1.20 for the primary endpoint of 90-day all-cause mortality, the key safety outcome of AKI, and the composite outcome of treatment failure. †Posterior probabilities are not reported for secondary outcomes, with the exception of the key safety outcome of AKI and the composite outcome of treatment failure. ‡Superiority was defined as an adjusted odds ratio of less than 1.00 for the primary endpoint of 90-day all-cause mortality and the key safety outcome of AKI. §These prespecified safety secondary outcomes were collected for all participants; numerators and denominators are provided to indicate where data was missing or unavailable. ¶Defined as an absolute creatinine increase of 26.5 µmol/L (0.3 mg/dL) or more within 5 days of platform entry or a relative increase of 50% or more from baseline within the first 14 days. ||Non-inferiority for this comparison only was defined as an adjusted odds ratio of less than 1.85 for the composite outcome of treatment failure. **Defined as alanine aminotransferase or γ-glutamyl transferase increasing above 2.5 times the upper limit of normal within 14 days.

Table 3: Primary and secondary outcomes

Research in context

Evidence before this study

We searched PubMed using the terms “penicillin-susceptible *Staphylococcus aureus*,” “PSSA”, “bacteraemia”, “penicillin G”, “benzylpenicillin”, and “antistaphylococcal penicillins” for studies published from database inception to May 1, 2024. The current standard treatment for penicillin-susceptible *Staphylococcus aureus* (PSSA) bacteraemia is an anti-staphylococcal penicillin, such as flucloxacillin. Several observational studies have reported similar or superior outcomes with benzylpenicillin compared with anti-staphylococcal penicillins in PSSA bacteraemia. However, these were subject to limitations, including confounding by indication and immortal time bias. International guidelines have continued to recommend anti-staphylococcal penicillins over penicillin for serious infections, due to historical concerns about undetected penicillin resistance. No previous randomised controlled trial has directly compared benzylpenicillin with anti-staphylococcal penicillins in PSSA bacteraemia.

Added value of this study

To the best of our knowledge, this is the first randomised controlled trial comparing benzylpenicillin with flucloxacillin or

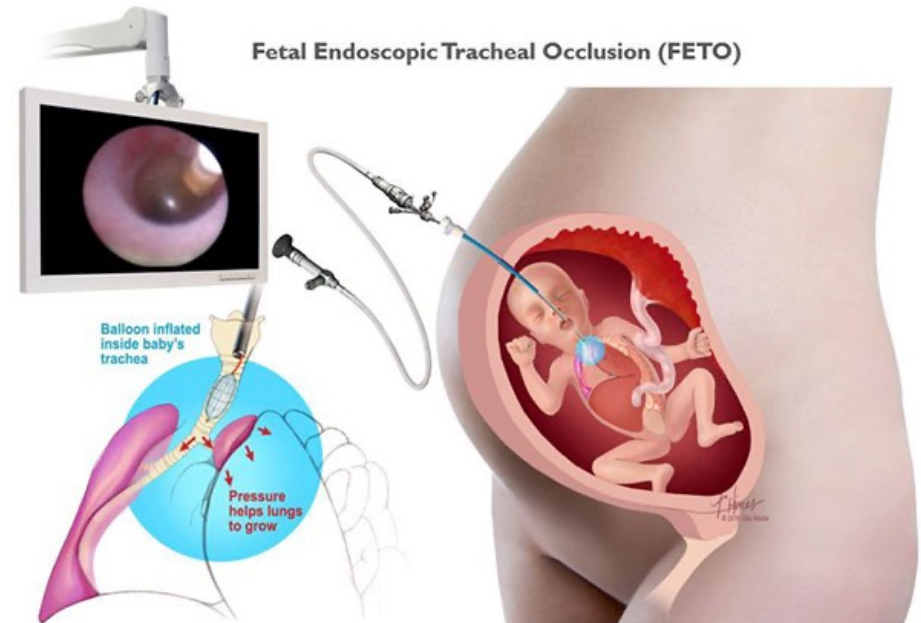
cloxacillin for PSSA bacteraemia. Conducted within the international *Staphylococcus aureus* Network Adaptive Platform, the trial enrolled 281 adults who were admitted to participating hospitals. Benzylpenicillin showed a posterior probability of non-inferiority of 96.1% and superiority of 88.9% for the primary outcome of 90-day all-cause mortality. Benzylpenicillin was also associated with lower rates of acute kidney injury. The results were consistent in intention-to-treat and protocol-adherent analyses. The trial also showed the feasibility and reliability of modern phenotypic penicillin-susceptibility testing of *S aureus* across multiple international sites.

Implications of all the available evidence

These findings suggest that benzylpenicillin is at least as effective as and is safer than flucloxacillin or cloxacillin for PSSA bacteraemia and therefore should be preferred over anti-staphylococcal penicillins for treatment for adults with PSSA bacteraemia, where accurate laboratory testing for penicillin susceptibility is available.

Cefazolin is cheaper and easier

Die fetoskopische endoluminale Trachealokklusion (FETO) ist ein spezialisierter, minimalinvasiver chirurgischer Eingriff, der noch während der Schwangerschaft am ungeborenen Kind (Fötus) durchgeführt wird. Das Verfahren dient der Behandlung einer schweren **angeborenen Zwerchfellhernie (Congenital Diaphragmatic Hernia, CDH)**. Durch das vorübergehende Blockieren der fetalen Luftröhre wird das Lungenwachstum des Babys gezielt angeregt, um dessen Überlebenschancen nach der Geburt maßgeblich zu verbessern.



New device permitting non-invasive reversal of fetal endoscopic tracheal occlusion: *ex-vivo* and *in-vivo* study

Objective

One of the drawbacks of fetal endoscopic tracheal occlusion (FETO) for congenital diaphragmatic hernia is the need for a second invasive intervention to re-establish airway patency. The 'Smart-TO' device is a new balloon for FETO that deflates spontaneously when placed in a strong magnetic field, therefore overcoming the need for a second procedure. The safety and efficacy of this device have not yet been demonstrated. The aim of this study was to investigate the reversibility, local side effects and occlusiveness of the Smart-TO balloon, both in a simulated in-utero environment and in the fetal lamb model.

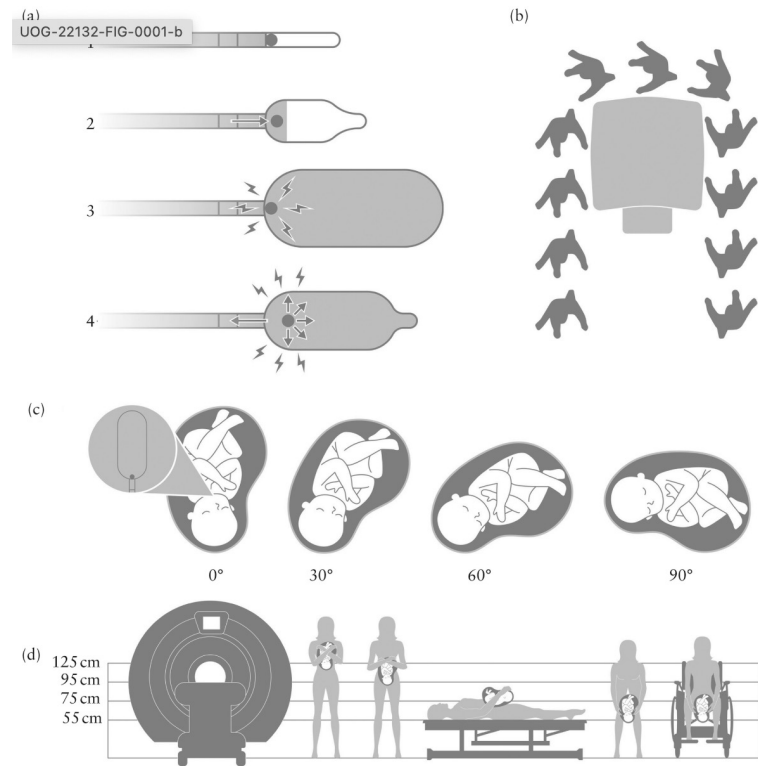


Figure 1

[Open in figure viewer](#) | [Download PowerPoint](#)

Diagrammatic representations of: (a) the Smart-TO balloon in its different states ((1) deflated; (2) inflating; (3) inflated; (4) deflating); (b) deflation protocol, showing view from above of simulated patient walking around MR scanner; (c) ex-vivo model simulating different fetal positions; and (d) simulated maternal scenarios and heights of fetal mannequin above ground.

Non-invasive removal of the Smart tracheal occlusion device for fetal congenital diaphragmatic hernia: a single-arm, open-label, phase 1 study

Summary

Background One of the drawbacks of fetoscopic endoluminal tracheal occlusion (FETO) for congenital diaphragmatic hernia (CDH) is the need for a second intervention to establish airway patency. In this first-in-human study, we aimed to evaluate a novel tracheal occlusion device (Smart-TO) that spontaneously deflates when in close proximity to a strong magnetic field.

Methods We conducted two parallel single-centre, single-arm, open-label trials in Paris, France, and Leuven, Belgium. Eligibility criteria included patient age 18 years or more, singleton pregnancy with CDH, and severe or moderate pulmonary hypoplasia in left-sided CDH; in Leuven, eligibility criteria also included severe hypoplasia in right-sided and bilateral CDH. Fetal lung size was assessed by measuring the observed-to-expected lung-to-head ratio by ultrasonography. Data for baseline demographics were self-reported and collected at the screening visit. Insertion of the Smart-TO balloon was scheduled between 27⁰ weeks and 31⁶ weeks of gestation. Balloon deflation was scheduled between 34⁰ weeks and 34⁶ weeks (or earlier, if clinically indicated) by exposure to the magnetic field of a MRI machine, and ultrasonography was then done to confirm balloon deflation. The primary endpoint was balloon deflation, with expulsion of the balloon from the fetal airways at birth as a coprimary outcome in the Paris arm of the study. The primary outcome was reported with its 95% CI using the continuity-corrected score method for all patients with the investigational medical device in place at the time of deflation. Safety analysis was conducted for all patients in whom FETO was attempted. These trials are registered with ClinicalTrials.gov (NCT04931212 [Paris]) and NCT05100693 [Leuven]) and have been completed.

Findings Between Aug 4, 2021 and Jan 15, 2024, 48 patients were enrolled. Of these, 47 patients underwent FETO, and the Smart-TO was successfully placed in 46 fetuses. Median gestational age at FETO was 29² weeks (28⁵–30¹ weeks). After placement, there was one spontaneous balloon deflation and one unexplained intrauterine fetal death. In all other patients, MRI machine-induced balloon deflation was attempted. The deflation rate was 100% (95% CI 92–100). At birth, the empty balloon was outside the airways in all infants. There were two cases of tracheomalacia in survivors, both with symptom resolution by the time of discharge from neonatal intensive care. There were 14 neonatal deaths, all attributed to pulmonary hypoplasia. Five adverse events were considered likely related to the device (of a total of 84), and no serious adverse events (of a total of 40) were related to the Smart-TO device.

Interpretation This study shows effective magnetic resonance-induced deflation of the Smart-TO balloon and supports short-term safety. These findings constitute an important advance in fetal surgery for CDH, eliminating the need for a second intrauterine procedure.

A magnet to avoid
a second operation

Introduction

Congenital diaphragmatic hernia (CDH) is a rare birth defect characterised by the failure of the diaphragm to close during the embryonic period. This failure of closure allows abdominal organs to herniate into the thorax, leading to pulmonary hypoplasia.¹ At birth, CDH causes respiratory failure and pulmonary hypertension, both potentially fatal. In isolated CDH, prenatal lung size and (in left-sided cases) intrathoracic liver herniation predict survival.²

For fetuses with a poor prognosis, fetoscopic endoluminal tracheal occlusion (FETO) stimulates lung growth, hence improving neonatal survival. FETO involves the percutaneous insertion of an off-label vascular occlusion balloon (Goldbal2; Balt, Montmorency, France) under maternal local anaesthesia.³ Balloon

removal is crucial to restore airway patency and is scheduled between 34⁺⁰ weeks and 34⁺⁶ weeks of gestation, or earlier if needed.⁴ Removal is typically done by fetoscopy or ultrasonography-guided puncture; when these methods are not possible, the balloon is removed after delivery while the fetus is on placental circulation or by postnatal puncture.^{4,5}

The randomised TOTAL trials^{6,7} compared survival with FETO versus expectant management in left-sided CDH with severe or moderate hypoplasia. In severe CDH, balloon insertion at 27⁺⁰ weeks to 29⁺⁶ weeks of gestation more than doubled neonatal survival (40% *vs* 15%; relative risk 2.67).⁸ In moderate CDH, whereby the balloon was inserted at 30⁺⁰ weeks to 31⁺⁶ weeks, the treatment effect was smaller (63% survival *vs* 50% survival; 1.27).⁹ Post-hoc analysis of the pooled data suggested that the lesser effect in moderate hypoplasia was likely a consequence of the later balloon insertion.¹⁰ A 2023 meta-analysis¹¹ confirmed that FETO reduces mortality in severe and moderate hypoplasia, and, in severe cases, also reduces pulmonary hypertension.

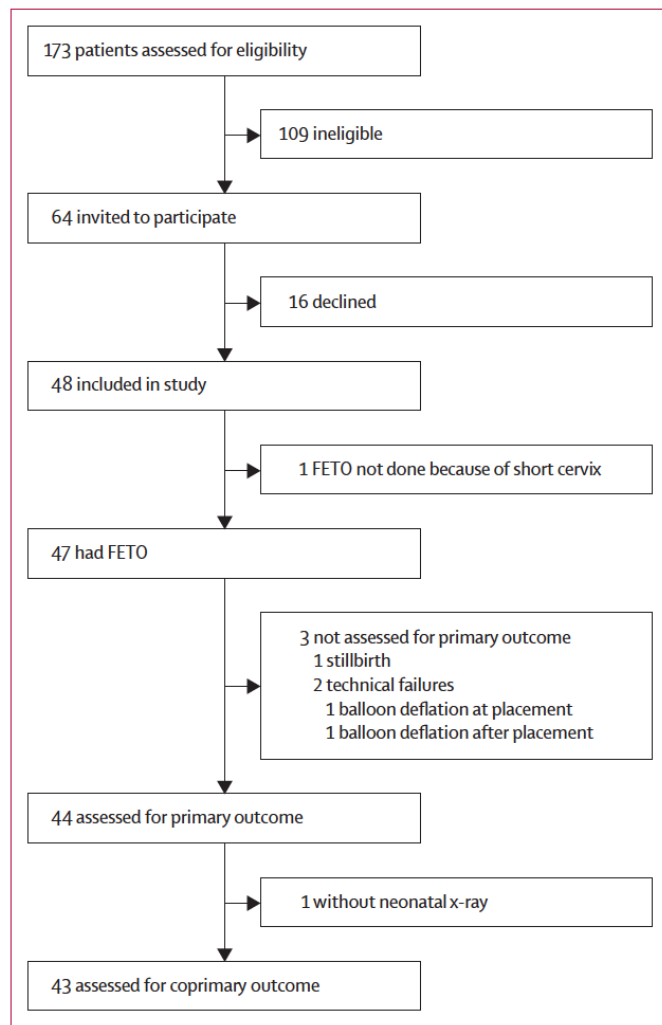


Figure: Study profile
FETO=fetoscopic endoluminal tracheal occlusion.

	Patient data (N=47)
Maternal age, years	31 (28–36)
Ethnicity	
White	38 (81%)
Black	5 (11%)
Asian	3 (6%)
Other	1 (2%)
Cigarette smoker	4 (9%)
Alcohol use during pregnancy	0
Spontaneous conception	40 (85%)
Nulliparous women	29 (62%)
BMI, kg/m ²	26.8 (23.4–30.8)
Gestational age at inclusion, weeks	28 ⁺ (27 ⁺ –29 ⁺)
No anomalies on genetic testing	44 (94%)*
Fetal sex	
Male	29 (62%)
Female	18 (38%)
Findings at ultrasound before FETO	
Sidedness of CDH	
Left	43 (91%)
Right	3 (6%)
Bilateral	1 (2%)
Observed-to-expected lung-to-head ratio, %†	
Left-sided CDH	29% (24–32)
Right-sided CDH	38% (19–41)
Intrathoracic liver herniation	
Left-sided CDH	38/43 (88%)
Right-sided CDH	3/3 (100%)
Bilateral CDH	1/1 (100%)
Stomach grade [‡] (left CDH only)‡	
1	1/38 (3%)
2	10/38 (26%)
3	10/38 (26%)
4	17/38 (45%)
Deepest vertical pocket of amniotic fluid, § cm	6.5 (5.2–7.7)
Cervical length, ¶ mm	37 (33–41)
Observed-to-expected total fetal lung volume on MRI, %	26.5% (21.0–31.0)
Placenta position	
Anterior	23 (49%)
Posterior	21 (45%)
Lateral	3 (6%)
Additional structural findings	5 (11%)

Data are median (IQR), n (%), or n/N (%). One fetus that did not undergo FETO was excluded from the analysis. CDH=congenital diaphragmatic hernia.
FETO=fetoscopic endoluminal tracheal occlusion. *One case of chromosome 10 deletion and one case of a truncating heterozygote deletion of 8q22.3q23.2 (ZFPM2 gene), inherited from the mother. †In the fetus with bilateral CDH, observed-to-expected lung-to-head ratio could not be measured, but observed-to-expected total fetal lung volume was 7%. ‡Ultrasound severity parameter, five patients with missing data. §Two patients with missing data. ¶Four patients with missing data. ||One fetus had a muscular cardiac ventricular septum defect, and one had pleural effusion, for which a thoracic shunt was placed at the referring centre before FETO; three had suspicion of bronchopulmonary sequestration or congenital pulmonary adenomatoid malformation.

Table 1: Baseline characteristics of the study population

	Patient data (N=47)
Balloon insertion	
Gestational age at procedure, weeks	29 ⁺ (28 ⁺ –30 ⁺)
Anaesthesia	
Local	25 (53%)
Neuraxial block	22 (47%)
Successful balloon insertion	46 (98%)
Amniodrainage	27 (57%)
Total in-utero time, min	9 (6–17)
In-trachea time, min*	4 (3–10)
Post-FETO follow-up†	
Spontaneous deflation	1/45 (2%)
Proportional change in observed-to-expected lung-to-head ratio between baseline and week 2, %*	38% (26–72)
Need for amniodrainage	7/45 (15%)
Occurrence of chorionic membrane separation	10/45 (22%)
Reversal of tracheal occlusion‡	
Deflation attempted	44/44 (100%)
Deflation successful	44/44 (100%)
Elective deflation	28/44 (64%)
Indication for earlier deflation	
PPROM	8/44 (18%)
Preterm labour	3/44 (7%)
Other§	5/44 (11%)
Gestational age at deflation, weeks	
All	34 ⁺ (33 ⁺ –34 ⁺)
At elective deflation	34 ⁺ (34 ⁺ –34 ⁺)
At earlier deflation	33 ⁺ (32 ⁺ –33 ⁺)

Data are median (IQR) or n/N (%). FETO=fetoscopic endoluminal tracheal occlusion. PPRM=preterm prelabour rupture of membranes. *Three patients with missing data. †One intrauterine fetal death and one patient in which the balloon could not be placed were excluded from the analysis. ‡A patient with spontaneous balloon deflation was excluded from the analysis in addition to the two patients already excluded. §One patient with contractions and maternal discomfort due to polyhydramnios; two patients with complete chorionic membrane separation; one patient with cervical shortening; and one patient with cervical shortening and chorionic membrane separation.

Table 2: Operative outcomes for the balloon insertion and removal procedure and period in between

Complication	
Leuven-013	Bending of catheter while being advanced into the trachea, probably due to manipulation; detachment of balloon during repositioning; removal of fetoscope, loading of new catheter and balloon; uncomplicated insertion of a new balloon
Leuven-019	Balloon emptied on detachment and empty balloon was retrieved; uncomplicated placement of new balloon; retrospectively: operator error, valve not tested before insertion in patient
Leuven-021	Balloon integrity confirmed at pretest; balloon emptied on detachment after insertion and detachment; empty balloon was retrieved; uncomplicated placement of new balloon
Leuven-022	Balloon integrity confirmed at pretest; balloon emptied on detachment after insertion and detachment; empty balloon was retrieved; uncomplicated placement of new balloon
Leuven-023	Backflow of fluid from the balloon was noted after positioning; retrieval of instruments and repositioning of the balloon on catheter; re-insertion without obvious backflow after filling or leakage after detachment; spontaneous deflation diagnosed on day 1 after FETO
Paris-004	Defective balloon with obvious leakage through hole after detachment; potential balloon damage while advancing the catheter; new balloon used, with uncomplicated placement
Paris-017	Balloon emptied on detachment and empty balloon was retrieved; two additional attempts were made to insert a new balloon, but the balloons emptied again at detachment; procedure was abandoned
Patients are identified by site and number. FETO=fetoscopic endoluminal tracheal occlusion.	
Table 3: Complications reported at insertion of the investigational medical device	

	Likely related to the device	Likely related to the FETO procedure	Likely unrelated to the device or to FETO
Adverse events	2*	6†	73‡
Serious adverse events	0	29§	11¶
Adverse events of special interest	3	0	0
FETO=fetoscopic endoluminal tracheal occlusion. PPROM=preterm prelabour rupture of membranes. *One need for a second fetoscopy to place a new balloon due to spontaneous deflation and one failed FETO due to an operator handling error (included in the list of complications at balloon insertion [table 3] but also reported as adverse events). †Balloon deflation before 34 weeks due to increased risk of preterm birth (n=5) and chorionic membrane separation without PPROM (n=1). ‡Includes polyhydramnios, pregnancy complications (hypertension, diabetes, cholestasis, and urinary tract infection), reduced fetal movements, complications during delivery and postpartum (anaemia, and mild postpartum bleeding) and neonatal complications mainly related to congenital diaphragmatic hernia. §Includes one intrauterine fetal death and cases of PPROM and/or preterm labour. ¶Includes polyhydramnios requiring hospitalisation, major postpartum bleeding or need of placental revision, severe neonatal complications due to congenital diaphragmatic hernia, and neonatal death. Includes two cases of tracheomalacia and one spontaneous balloon deflation.			
Table 5: Adverse events			

Patient data (N=44)	
Gestational age at PPROM, weeks	34 ⁻¹ (32 ⁻⁵ –36 ⁻⁵)
PPROM	
<37 weeks	21 (48%)
<32 ⁻⁶ weeks	4 (9%)
32 ⁻⁶ to 33 ⁻⁶ weeks	6 (14%)
34 ⁻⁶ to 36 ⁻⁶ weeks	11 (25%)
Gestational age at delivery, weeks	37 ⁻² (34 ⁻⁴ –38 ⁻²)
Preterm birth	
<32 ⁻⁶ weeks	1 (2%)
32 ⁻⁶ to 33 ⁻⁶ weeks	8 (18%)
34 ⁻⁶ to 36 ⁻⁶ weeks	11 (25%)
Mode of delivery	
Vaginal	25 (57%)
Caesarean section	18 (41%)
Ex-utero intrapartum treatment	1 (2%)
Birthweight, g	2710 (2358–3026)
Balloon localisation at birth	
Newborn: airways	0
Newborn: gastrointestinal tract	19 (43%)
Newborn: other location	1 (2%)
Placenta or membranes	0
Uterus	0
Not visualised	24 (55%)
Survival at discharge from NICU	
Overall	30 (68%)
Left-sided CDH	29/40 (73%)
Right-sided CDH	1/3 (33%)
Bilateral CDH	0/1
Reported cause of death	
Respiratory insufficiency	6/14 (43%)
Pulmonary hypertension	5/14 (36%)
Multiorgan failure	3/14 (21%)
Duration of NICU hospitalisation in survivors, days	45 (57–75)
Signs or symptoms of tracheomalacia in survivors	2/30 (7%)
Persisting tracheal symptoms	0/30
Data are median (IQR), n (%), or n/N (%). CDH=congenital diaphragmatic hernia. NICU=neonatal intensive care unit. PPROM=preterm prelabour rupture of membranes.	
Table 4: Perinatal outcomes	

Research in context

Evidence before this study

The TOTAL trials provided level-1 evidence that fetoscopic endoluminal tracheal occlusion (FETO) with a balloon improved survival in selected cases of left-sided congenital diaphragmatic hernia (CDH). Meta-analyses have since confirmed this finding, and the same treatment effect is suggested for severe right-sided CDH. However, the need for a second intervention to remove the balloon is a major drawback due to the additional feto-maternal risk and substantial logistical burden on patients and treatment teams. Moreover, the inability to free the fetal airways can be fatal. Preclinical ex-vivo and in-vivo studies have shown the safety and efficacy of the Smart-TO balloon, a device that is identical in dimensions to the device used previously for FETO but which can be deflated by exposure to the magnetic field around a clinical MRI machine.

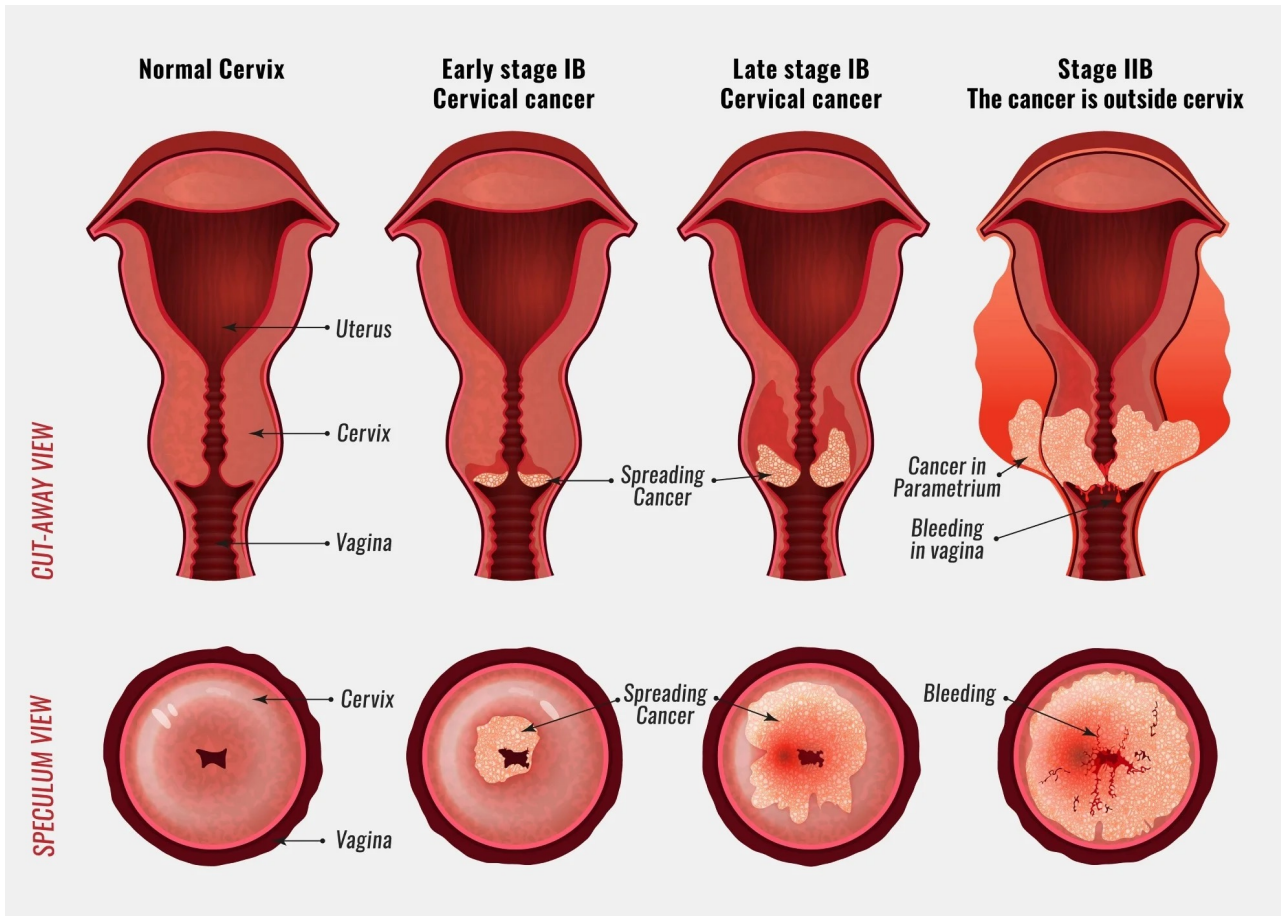
Added value of this study

To our knowledge, this study is the first phase 1 study in humans to evaluate the safety and efficacy of Smart-TO balloon

deflation on exposure to the fringe field of a clinical MRI machine. Deflation was successful in 100% of cases, and there were no severe balloon-related fetal or maternal adverse events. The survival rate in this cohort was 68%, and median gestational age at delivery was 37⁺² weeks (IQR 34⁺⁴ to 38⁺²). These results suggest that avoiding a second invasive procedure might reduce the risk of preterm birth and improve outcomes.

Implications of all the available evidence

FETO is an evidence-based fetal treatment option for selected CDH cases. Our study findings support the further safe clinical implementation of the Smart-TO balloon. This innovation marks an important advance in fetal surgery for CDH as it precludes the need for a second intrauterine surgery and avoids the associated risks, reducing the burden for patients and treatment teams and potentially improving outcomes.



Cervical cancer mortality trends following HPV vaccination in England, 2001–24: an analysis of population-based mortality data

Does HPV vacc. help?

Summary

Background Human papillomavirus (HPV) vaccination is a key component of global cervical cancer elimination strategies. While substantial declines in cervical cancer incidence have been observed in several countries, evidence of its effect on mortality is scarce. England introduced a national HPV vaccination programme in 2008 for girls aged 12–13 years (achieving 80–90% coverage before the COVID-19 pandemic), with a catch-up campaign in 2008–10 for girls aged 14–18 years. We aimed to investigate trends in cervical cancer mortality and to estimate the reduction in cervical cancer deaths in young women in England following the introduction of HPV vaccination.

Methods We analysed population-based cervical cancer mortality data from England between 2001 and 2024 among women aged 20–24, 25–29, and 30–34 years. HPV vaccination coverage by birth cohort was obtained from official reports and used to estimate, for each age group and calendar year of death, the proportion of women who had been vaccinated. We plotted observed and adjusted age-specific mortality rates against year of death and overlaid a smoothed curve. Poisson regression applied to the numbers of deaths was used to estimate the relative risk reduction in vaccinated women compared with what was expected in the absence of vaccination, assuming no herd immunity. Confidence intervals were obtained by inverting the likelihood ratio test.

Findings In women aged 20–24 years between 2020 and 2024, in whom vaccination coverage was around 88–90% at age 12–13 years, no deaths occurred, compared with 23·1 expected deaths based on historical rates, corresponding to a mortality reduction of 100% (95% CI 84–100). In earlier birth cohorts, who were offered vaccination up to age 18 years with coverage of around 63–87%, mortality reductions of 80% (51–94) in women aged 20–24 years in 2015–19, and 69% (55–79) in women aged 25–29 years in 2020–24 were observed. The relative risk reduction in vaccinated women was estimated from population-level data to be 100% (95% CI 81 to 100) in women aged 20–24 years, 100% (89 to 100) in those aged 25–29 years, and 63% (–13 to 100) in those aged 30–34 years. Up until the end of 2024, HPV vaccination in England was associated with a reduction of around 199·6 cervical cancer deaths (95% CI 125·0–274·2).

Interpretation Our findings provide the first robust national-level evidence, albeit observational, that high HPV vaccination coverage is associated with a substantial reduction in cervical cancer deaths. This is shown by the substantial decrease in cervical cancer deaths observed among women aged 20–29 years in England, particularly among those vaccinated at ages 12–13 years. These findings support the achievability of the WHO goal of eliminating cervical cancer as a public health problem, and efforts should be made to achieve high vaccine uptake among young adolescents globally.

Funding Cancer Research UK.

	Age 20–24 years			Age 25–29 years			Age 30–34 years		
	Deaths	Women-years (millions)	Rate per 100 000 women-years	Deaths	Women-years (millions)	Rate per 100 000 women-years	Deaths	Women-years (millions)	Rate per 100 000 women-years
Year of death									
2000*–04	25	7.72	0.32	59	8.22	0.72	171	9.59	1.78
2005–09	16	8.49	0.19	88	8.63	1.02	141	8.57	1.65
2010–14	27	8.95	0.30	123	9.22	1.33	145	9.06	1.60
2015–19	5	8.95	0.06	73	9.63	0.76	140	9.75	1.44
2020–24	0	8.54	0.00	32	9.59	0.33	131	10.33	1.27
Vaccination coverage									
	None 1–50% 51–87% 88–91%								

Figure 1: Age-specific mortality counts, women-years, and crude rates for 2000–24 by 5-year period of death

Shading indicates HPV vaccination coverage (appendix p 1). HPV=human papillomavirus. *Data for 2000 refer to England and Wales combined and are shown here for completeness only, but were not used in the regression analysis; note that since the population of Wales is about 5.5% of that of England, the death counts from Wales in 2000 are expected to be approximately one death in women aged 20–29 years (combined) and two in women aged 30–34 years.

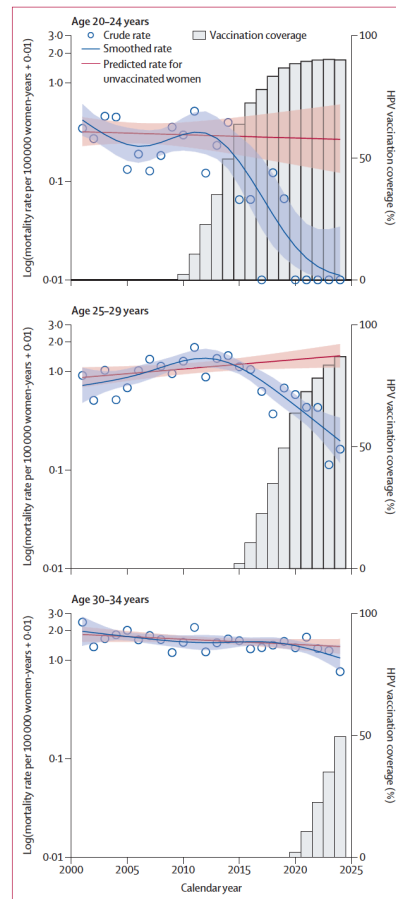


Figure 2: Age-specific scatter plots of crude mortality rates by year of death, including smoothed curves and predicted rates for unvaccinated women. Rates are displayed on a log scale after adding a small constant (since the logarithm of zero is undefined). Shaded regions are 95% CIs for the smoothed and predicted mortality rates. Bars show the proportion of women (in that age group and in that calendar year) who had been vaccinated against HPV during adolescence. In each age group, vaccination in the first 4 years of non-zero coverage was done when the recipients were aged 15–18 years and might therefore already have been exposed to HPV, and thus the effectiveness of vaccination is expected to be lower in these years. The smooth curve was obtained using a simple Poisson regression model with a restricted cubic spline for calendar year and no adjustment for vaccine coverage. The predicted rates in unvaccinated women were derived from the Poisson regression model used to estimate the relative risk reduction in vaccinated women. HPV=human papillomavirus.

	Age 20–24 years			Age 25–29 years			Age 30–34 years		
	No RRR	Estimated RRR	Perfect RRR	No RRR	Estimated RRR	Perfect RRR	No RRR	Estimated RRR	Perfect RRR
RRR* (95% CI)	0%	100% (81 to 100)	100%	0%	100% (89 to 100)	100%	0%	63% (–13 to 100)	100%
Pearson goodness-of-fit	40.59	26.67	26.67	77.85	31.33	31.33	21.66	19.41	21.22
Log likelihood	–46.79	–41.16	–41.16	–93.00	–69.23	–69.23	–73.22	–71.82	–72.64
p value†	..	0.0008	..	..	<0.0001	..	..	0.094	..

The no RRR columns show values when the relative risk (θ) is set at 1, corresponding to the null hypothesis that there is no effect of HPV vaccination on cervical cancer mortality. The perfect RRR columns show values when θ is set at 0, corresponding to the alternative hypothesis that women vaccinated against HPV have no risk of dying from cervical cancer (ie, the vaccination works perfectly). RRR=relative risk reduction. *RRR in cervical cancer mortality in vaccinated women, defined as $1-\theta$, expressed as a percentage; θ in vaccinated women is estimated assuming no herd protection in unvaccinated women. †H0: no effect of HPV vaccination ($\theta=1$).

Table: Estimated RRR in cervical cancer in vaccinated women and model fit in each age group

Research in context

Evidence before this study

Human papillomavirus (HPV) vaccination has been shown in randomised controlled trials to prevent persistent HPV infection and high-grade cervical intraepithelial neoplasia. Observational studies have also provided robust evidence that, in real-world settings, cervical cancer incidence has been reduced both in women vaccinated against HPV and in cohorts with high levels of HPV vaccine uptake. However, to date, very little empirical data have shown that HPV vaccination reduces deaths from cervical cancer. We used ChatGPT to search for “papers that report reduced cervical cancer mortality following HPV vaccination”. It yielded one research letter on trends in cervical cancer mortality in the USA in women aged 20–24 years, two studies linking HPV vaccination to reduced cervical cancer incidence, and two modelling studies that predict mortality reductions. We then searched PubMed for papers citing the research letter. This search returned ten papers, none of which provided further evidence on cervical cancer mortality following HPV vaccination. An additional search in PubMed using “(HPV vaccination) AND (cervical cancer) AND (mortality OR deaths) AND rates” restricting to “clinical study” or “clinical trial” or

“observational study” identified 15 papers; however, these papers did not report on the observed impact of HPV vaccination on cervical cancer mortality.

Added value of this study

This study shows substantial reductions in cervical cancer mortality in England among women aged 20–29 years following the introduction of the national HPV vaccination programme. The lower limit of the 95% CI for the relative reduction in the risk of death from cervical cancer in vaccinated women is over 80% in the 20–24 years and 25–29 years age groups. No deaths from cervical cancer among women aged 20–24 years occurred in England during the last 5 years of our study follow-up (2020–24).

Implications of all the available evidence

These data suggest that HPV vaccination programmes for adolescent females can lead to reduced deaths from cervical cancer, reinforcing the importance of achieving and maintaining high vaccination coverage, particularly in females aged 12–15 years (while most are still sexually inactive).

Children in all policies: lessons from a global collaboration to promote the health and wellbeing of children and future generations

Currently children's needs, perspectives, and rights are not adequately included in public policies, with negative consequences for the health and wellbeing of children and future generations. The 2020 WHO–UNICEF–*Lancet* Commission reviewed threats to children's health and concluded that children's needs and voices should be centred in all policies for a sustainable future. Since 2021, Children in All Policies 2030, a global collaboration of policy makers, scientists, and advocates, has implemented the Commission's recommendations by fostering new approaches to participatory, intersectoral policy making across diverse countries. Efforts to implement the Commission's recommendations encountered challenges including flawed assumptions in prevailing policy-making models, failure to fulfil children's right to participate, and an ongoing scarcity of intersectoral policy integration. Eight lessons on what works for improving policy making and implementation emerged: use creative means to involve children, patiently assemble coalitions, prepare to seize political opportunities, harmonise global data to bridge UN partnerships, create national political and technical platforms, use media to change cultural perceptions, use strategic framing to overcome sectoral barriers, and embrace joint learning. Harnessing people's consideration and concern for children and future generations and engaging children's voices represents a powerful political opportunity to reach current development goals and ensure a healthier, more sustainable future.

Future of world's children?

Panel 1: Key messages of the 2020 WHO–UNICEF–Lancet Commission report

In February, 2020, the WHO–UNICEF–Lancet Commission published its report *A future for the world's children?*,⁸ which called for placing the health and wellbeing of children and adolescents at the centre of national and global efforts to achieve sustainable development. Early investments in children's health, development, and education create benefits across children's lifetimes, as well as for future generations and society as a whole. As such, the report argued that decision makers need apply a long-term vision and mobilise funding, particularly for the poorest families and children. Social action and the participation of citizens, including children themselves, are crucial to buttressing political efforts to fulfil children's entitlements and mobilise the resources needed to reach the UN Sustainable Development Goals.

Children's rights, enshrined in the UN Convention on the Rights of the Child in addition to many national frameworks, encompass entitlements across all sectors, including health and education but also housing, agriculture, energy, transport, and more. A deliberately intersectoral approach is needed to ensure children survive and thrive. Actions might take different forms in each country but require coordination across ministries, strategic partnerships with diverse collaborators, and strong political leadership. The fragmented provision of resources at global level must be streamlined to support joined-up strategies, budgets, and implementation.

The report called for measuring children's flourishing across domains (including survival, development, mental health and wellbeing, educational achievement, safe and clean environments, and protection from violence) using improved data, starting with better collection of the child-related Sustainable Development Goal indicators, many of which fewer than 50% of countries worldwide report data for. Using a measure of children's current and future wellbeing that encompasses greenhouse gas emissions and the equitable distribution of wealth, not one single country performed well across all dimensions (flourishing, sustainability, and equity). In addition to stronger national systems, citizen accountability mechanisms were recommended to fill data gaps, alongside the development of user-friendly country dashboards to provide a holistic view of children's health and wellbeing.

In addition to ecological threats, the report analysed emerging commercial threats to children's health, notably their enormous exposure to marketing for harmful products including sugar-sweetened beverages, alcohol, tobacco, and gambling products, which are major causes of non-communicable diseases and other threats to health and wellbeing. Commercial actors not only target children with marketing techniques that exploit their developmental vulnerability but also harvest their data, raising major privacy concerns. The Commission called for the development of new international legal instruments to regulate against commercial marketing to children and protect them from other commercial harms.

Finally, children and adolescents' right to participate in decisions that affect them frequently goes unfulfilled. Yet it is a powerful tool in efforts to enact policies to deliver a healthy and sustainable future. The Commission called for children to be placed at the heart of a new global movement to promote their health and future on this planet.

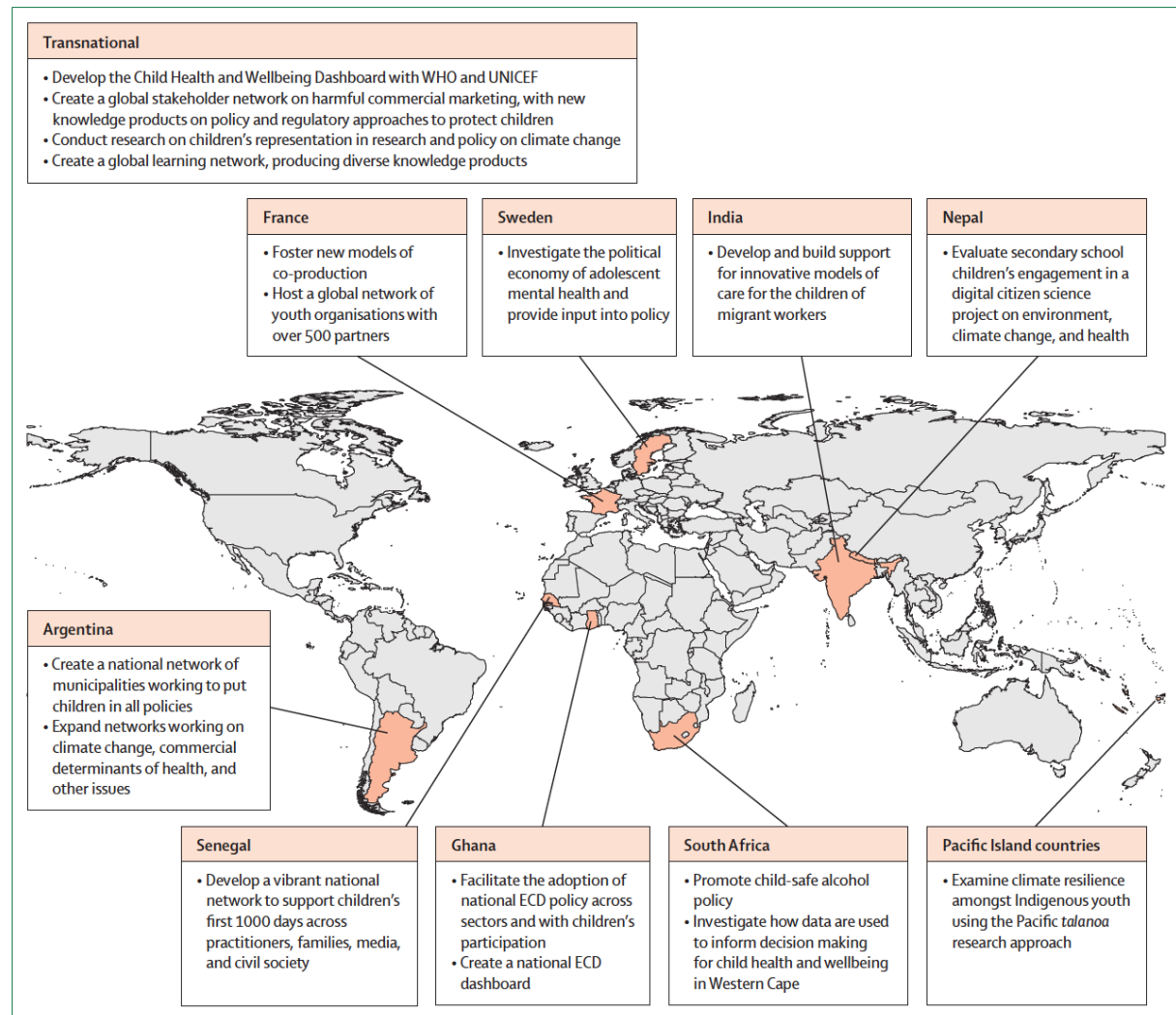


Figure 1: Research, advocacy, and implementation undertaken by members of the Children in All Policy 2030 consortium
ECD=early childhood development.

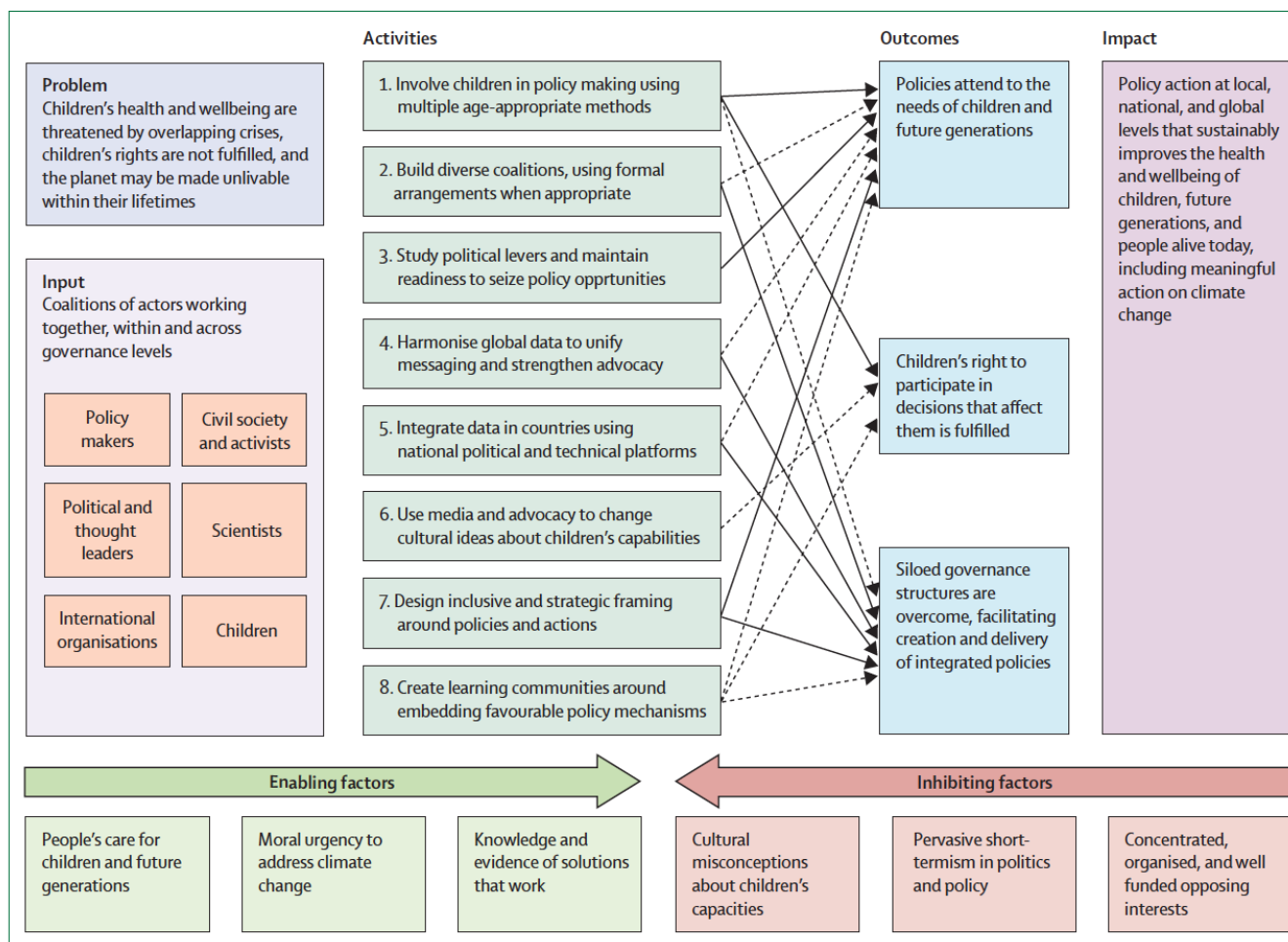


Figure 2: Theory of change of the Children in All Policy 2030 consortium
Solid arrows show observed pathways and dashed arrows show hypothesised pathways.



Figure 3: Children and policy makers at the Children in All Policy 2030 national policy workshop (September 2021, Ghana)

Image provided by the Center for Learning and Childhood Development, Ghana.

Panel 2: Children in All Policies 2030 Youth Advisory Board and meaningful youth engagement

In 2023, 22 adolescents age 13–18 years were selected from more than 90 applicants to participate in the Children in All Policies 2030 (CAP-2030) Youth Advisory Board (YAB). The term youth was selected in the name to emphasise participants' maturity rather than their status as legal minors. Members hailed from 18 countries and were selected with a view of ensuring balanced membership in terms of gender, socioeconomic and racial background, and geography. The YAB met online in small groups and in plenary over the course of a year, providing input on CAP-2030's core areas of work, including data for decision making, climate change, harmful commercial marketing, and racism and child health. They participated via surveys and focus group discussions, writing blogs, creating PowerPoint presentations, and interacting with high-level officials at WHO, UNICEF, and other international bodies. Engagement was structured to promote meaningful co-creation, and YAB members received feedback on how their inputs were used and the outcomes of their work.

The YAB substantively shaped CAP-2030's activities, strategy, outputs, and communications: they shaped findings on future research priorities on climate change, revised an interview guide on racism and child health to make it more intersectional, and introduced new focus industries for work on harmful marketing.⁵⁹ YAB members have spoken on behalf of CAP-2030 in major public forums and served as named authors on reports and scientific publications, including this Health Policy.

CAP-2030's experience with the YAB further supports the notion that involving children earlier in policy-making processes and affording them greater control over strategic direction is crucial to gaining the full benefits of their participation. Indeed, although taking input from children is preferable to not engaging with them at all, arguably only co-creation and other forms of power-sharing meaningfully fulfil the obligations of the UN Convention on the Rights of the Child.⁶⁰

Panel 3: Building coalitions to oppose harmful commercial marketing to children

Commercial enterprises use marketing to promote sales and increase brand influence of unhealthy products, threatening children's health and wellbeing through immediate consumption, habit formation that impacts the entire life course, and the marketing techniques themselves.⁶¹ Companies in the tobacco, alcohol, ultra-processed food, sugar-sweetened beverage, and gambling industries all market to children, an immensely profitable investment given the billions of dollars in spending that children influence directly and indirectly.⁶² Governments are increasingly adopting policies to reduce harmful marketing to children using different legislative and regulatory tactics. But where policies' costs affect a small number of powerful actors, namely business corporations in concentrated industries, these actors tend to organise collectively to advocate for their interests.⁴¹ Conversely, given these policies' more diffuse public benefits, lobbying and campaigning efforts to support them are often undersupplied.

Members of the Children in All Policies 2030 (CAP-2030) consortium worked to build coalitions to counter harmful marketing in three main ways. First, research was conducted to highlight the harms of commercial marketing to children and assess policy and regulatory strategies that can be used to reduce those harms in countries around the world.^{61,62} To expand the network of scientists working on these issues, sessions were organised at paediatrics conferences, training for health professionals was supported, and working groups were built within global paediatric associations. Second, advocacy was used to increase public understanding of the harms of commercial marketing to children and high-profile public webinars and events were hosted, with the inclusion of children and with accompanying videos, social media campaigns, and general-interest publications, including explanations using child-friendly language. Third and perhaps most importantly, global stakeholder networks were organised to protect children's rights from harmful marketing. In 2021, CAP-2030 co-hosted a 3-day virtual conference with WHO, UNICEF, and The Office of the United Nations High Commissioner for Human Rights that gathered 90 international experts on public health and children's rights including policy makers, lawyers, health professionals, and technical specialists. Participants agreed upon a set of short-term and medium-term objectives for reaching high-level goals, focusing on how the international health and child rights community, civil society organisations, and policy makers can work towards stronger and more comprehensive action in tackling the issue of harmful marketing and protecting children. To implement this plan, WHO is leading a mistakeholder group to help countries strengthen legal and regulatory frameworks, with the active participation of adolescents and young people.

Despite growing recognition of the harmful effect of commercial marketing, commensurate funding to support action to protect children's health and wellbeing has not been seen. Many of the largest funding sources in global health are private foundations created to distribute fortunes amassed by the heads of large commercial corporations; their founders and managers might be ideologically opposed to limiting the activities of commercial actors in the so-called free market. Recognising the political and financial obstacles that hinder an agenda that benefits so many, CAP-2030 continues to seek partners to join and support our coalition to protect children from harmful commercial activity, including commercial marketing.

Panel 4: Lessons from the Future Generations Act in Wales

The Wales Future Generations Act, adopted in 2015, is the first piece of legislation in history to put sustainable development at the heart of government, incorporating not only environmental and economic issues but also culture, the arts, and the social sphere. Before the bill became law, thousands of Welsh people of all ages (including children) participated in a 1-year conversation called The Wales We Want, in which they defined the Wales they wanted to leave behind for their children and grandchildren. Climate change emerged as a crucial issue, alongside topics such as employment, education, health, and the value of park, leisure facilities, and libraries. Seven foundational principles emerged, summarised here as:

- 1 Children deserve the best start in life
- 2 Thriving communities are built on a strong sense of place
- 3 Valuing the environment means living within planetary limits and managing resources
- 4 The wellbeing of future generations depends on investing in local economy
- 5 Reducing inequality and valuing diversity are essential to ensuring the wellbeing of all
- 6 A strong citizen voice in decision making is fundamental to the democratic process
- 7 Valuing heritage, culture, and language will strengthen identity for future generations

These principles influenced the seven statutory wellbeing goals that public bodies are required to maximise, as well as the set of indicators used to monitor progress. The Act also sets out specified ways of working, including taking a long-term perspective and adopting an integrated, collaborative, and participatory approach. All public bodies under the Welsh Government are legally obligated to report on progress annually. The Act also created an independent Future Generations Commissioner, who serves as a guardian of future generations and monitors the extent to which wellbeing goals are being met. Civil society coalitions built up during the preparatory work to passing the Act have also proved influential in keeping public attention and action focused on its objectives.

Although Wales still has many historical challenges that need time to turn around, since its adoption, the Act has been credited with a suite of positive developments aimed at holistically improving wellbeing. For example, instead of building the proposed M4 ring road, a project with substantial political support, investment was made in a sustainable network of bicycle lanes, rail stations, and bus routes. Public sector food procurement has also been shifted to healthier, more sustainable sources, alongside a decision in favour of free universal school meals in primary schools. Key lessons suggest that the most effective path forward can be through pursuing embeddedness, that is, by mainstreaming long-term interests into day-to-day decision making and joining different policies, government bodies, and sectors, making the pursuit of all elements of wellbeing the responsibility of all.

Wales's Future Generations model has proved globally influential: "What Wales is doing today, the world will do tomorrow", Nikhil Seth, UN Assistant Secretary General said in 2015.⁸⁴ Indeed, movements are building to support similar legislation in Brazil, Denmark, Kenya, Ireland, Norway, Portugal, and Spain, and the world's first Indigenous Future Generations Commission was recently appointed in Mbessa, Cameroon. Principles and lessons from the Future Generations Act inspired the UN's 2024 Summit for the Future and resulting Pact for the Future, to be revisited at the 83rd UN General Assembly in 2028.⁸⁵

Panel 5: Extending the right to vote to children younger than 18 years

Arguments in favour of children being allowed to vote have been advanced since at least the 1970s on the basis of children's established capacity to cast meaningful votes, the value of encouraging early political participation, and the societal benefits of improving policy outcomes and resolving issues of justice.⁹¹ Yet children younger than 18 years can currently vote in approximately 14 countries, usually beginning at age 16 years. In 2025, the UK Government said that the voting age will be reduced to 16 years for all elections.⁹² Some countries place additional conditions and restrictions or allow children to vote in local elections only.

Arguments against lowering the voting age focus on children's lesser capacity and knowledge of politics, assumptions that are demonstrably unfounded, at least in the case of older adolescents.⁹³ Indeed, a convincing philosophical rationale exists for even removing the lower age bound to voting, given the absence of strong reasons to override the presumptive right to vote.^{94,95} Under some proposals, all children gain a vote, with parents or guardians exercising a proxy vote for younger children.⁹⁶ Extending the franchise even just to older children and adolescents would reap substantial democratic dividends, as people excluded under the current voting age comprise approximately one-fifth of the total population in European, North American, and Australian democratic states and nearly one-half of the population in Africa, Asia, and South America.⁹¹

Allowing children to vote enables them to make decisions for themselves, an important fulfilment of child rights, and will arguably result in improvements in health outcomes, as children can vote to improve the determinants of their health; for example, living conditions and education. Children's voting might also incentivise parliaments to take a long-term perspective on issues, although evidence needs to be collected on any changes that are made.

Incremental change might be more politically palatable and could constitute a starting point for the substantial political organising that will be required among both children and adults, as the status quo is currently aligned against children voting. Further research can support efforts to shift social and cultural norms to promote the idea of lowering the voting age in countries worldwide.

	Description	Considerations to enhance inclusivity
Establish youth advisory boards to provide direct input on policy decisions at all levels of governance	Require clear mandates, legal recognition, and structured mechanisms for youth participation in policy formulation and review; institutionalise platforms using legislation and dedicated funding to ensure continuity, accountability, and influence over policy making	Ensure fair and transparent selection to include diverse youth from all backgrounds, including rural and under-represented communities; budget for accessibility measures such as sign language interpretation, Braille documents, remote participation options, and translation and interpretation
Embed youth consultations into policy development from ideation to implementation and evaluation	Establish structured, transparent, and action-oriented consultation frameworks that ensure youth perspectives lead to tangible policy changes; require policy makers to provide written or public responses outlining how youth input influenced policy decisions, to enhance accountability and build credibility in youth participation efforts	Simplify policy discussions using accessible and youth-friendly formats that break down complex information into digestible insights; offer flexible participation options to allow students, workers, and those from remote areas to contribute without major disruptions to their daily lives
Use diverse, culturally aware outreach to help youth understand policy impacts	Leverage youth-friendly platforms such as social media, digital storytelling, and interactive campaigns with content creators that simplify complex policy information into accessible, engaging content; implement offline outreach strategies, such as community forums, youth town halls, and school-based discussions in communities that do not have access to online platforms	Ensure outreach materials are translated into local languages and use accessible formats for youth with disabilities; build trust with marginalised communities as they might view institutions with scepticism due to previous experiences of neglect or discrimination
Support the further development of youth leadership in policy spaces	Invest in structured youth leadership development programmes that equip youth with advocacy, negotiation, and decision-making skills; provide hands-on experiential learning opportunities, such as internships, fellowships, and youth delegate programmes, to provide exposure to policy-making environments	Include mentorship programmes where experienced policy makers, researchers, and youth activists guide marginalised youth in navigating governance systems
Adapt policies based on youth feedback and real-world impact	Establish clear evaluation frameworks that track youth participation, policy responsiveness, and overall impact; develop a public Youth Policy Scorecard, where youth-led organisations and independent watchdogs can track policy progress and identify gaps	Integrate equity and inclusivity metrics into evaluation frameworks

Table: Actionable strategies for youth-inclusive governance proposed by the Children in All Policy 2030's Youth Advisory Board

Conclusion

For too long, political and policy-making paradigms have abruptly dismissed the rights and perspectives of children and future generations, a situation only worsened by today's overlapping crises. Society cannot, from an ethical, economic, or ecological standpoint, continue to discount the future to the detriment of posterity. Based on the children in all policies vision, CAP-2030 is developing new models, methods, and measurement tactics for investing in children and future generations—bridging a new frontier in participatory, intersectoral policy making. Prevailing development paradigms are not meeting the challenges facing children today and future generations to come. We continue to believe that our message—centring children for sustainable policies in all sectors—is powerfully mobilising. We welcome new partners and contributors in research, policy, and practice to fulfil our commitment to children and future generations.

A case of acute necrotising encephalitis secondary to human herpesvirus 6 infection

In this Clinical Rounds, we present the case of a girl aged 11 months who developed acute necrotising encephalitis in the setting of human herpesvirus 6 infection, complicated by elevated intracranial pressure, seizures, and development of increased tone. This patient presented with common features of acute necrotising encephalitis including fever, seizures, altered level of consciousness, and focal neurological deficits. We discuss the investigations for acute necrotising encephalitis, which is extensive and includes serology, often showing thrombocytopenia and liver dysfunction. Cerebrospinal fluid studies can show elevated protein without pleocytosis of white blood cells. Imaging can show signal intensity changes on T2-weighted images in the bilateral thalami, basal ganglia, subcortical white matter, cerebellum, and brainstem, in addition to restricted diffusion. In this Clinical Rounds, we also highlight the importance of rapid treatment, which includes immunosuppression with corticosteroids, intravenous immunoglobulin, and plasma exchange. Finally, we discuss the poor outcomes and prognosis for patients diagnosed with acute necrotising encephalitis, with a 27% mortality rate and moderate to severe disability in 63% of survivors.

Learning points

- Acute necrotising encephalitis is a rapidly progressive neurological disorder that is most common in children, often following a febrile illness (frequently influenza).
- Presenting symptoms of acute necrotising encephalitis often include fever, encephalopathy, seizures, and focal neurological deficits.
- MRI reveals diffuse bilateral and symmetric signal intensity changes on T2-weighted imaging and abnormalities on diffusion-weighted and susceptibility-weighted imaging. Apparent diffusion coefficient images often show a characteristic trilaminar appearance of the thalamus.
- Rapid immunosuppressive therapy within the first 24–32 h, with corticosteroids, interleukin-6 blockade, and plasma exchange, likely improves outcomes.

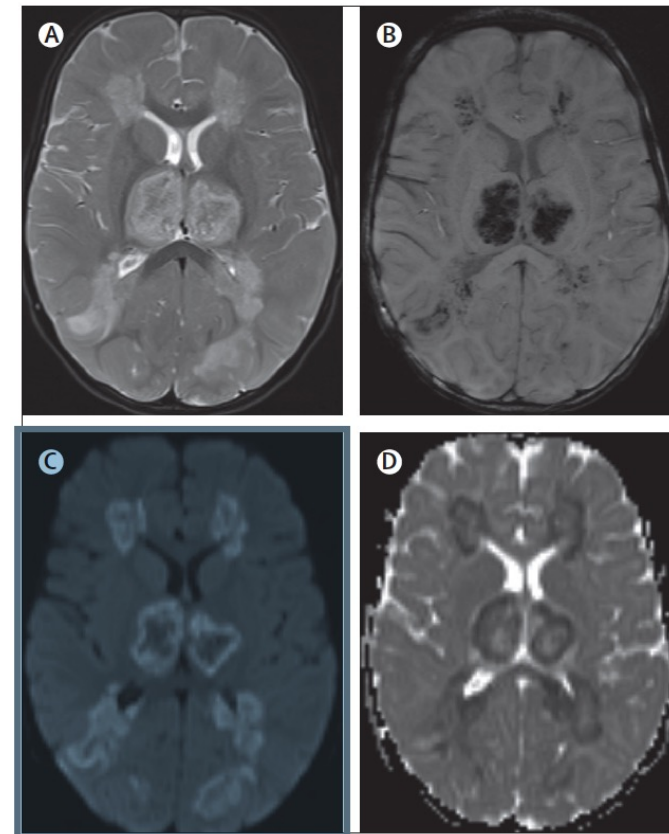


Figure: Head imaging of acute necrotising encephalopathy in an 11-month-old girl
(A) T2 image showing bilateral and symmetric thalamic and white matter changes. (B) Susceptibility-weighted image showing likely haemorrhagic necrosis. (C) Diffusion-weighted image showing concentric pattern of diffusion restriction of the thalami. (D) Apparent diffusion coefficient image showing trilaminar appearance of the thalamus with hyperchoic outer ring, hypoechoic middle layer, and hyperchoic centre.

Patient presentation

An 11-month-old unvaccinated girl, previously healthy and reaching normal developmental milestones, was admitted to hospital after 2 days of fever that progressed to vomiting and diarrhoea. Subsequently, she was noted to have an episode of upward eye deviation with bilateral decorticate posturing lasting approximately 30–60 s, during which she was not responsive to verbal or tactile cues. The patient was then transported to the emergency department, where another similar episode was witnessed upon presentation. She received treatment with levetiracetam load and midazolam for suspected seizures.

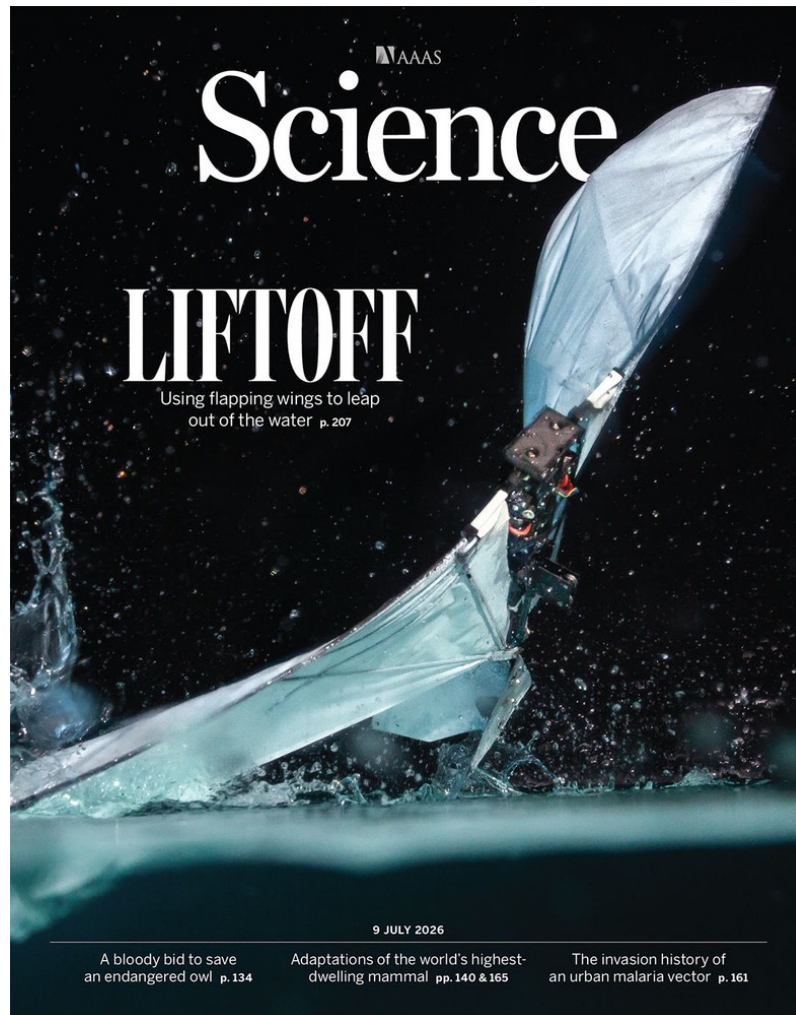
Conclusion

This patient presented with a diagnosis of acute necrotising encephalitis, a rare disorder with a broad differential diagnosis. In this Clinical Rounds, we highlighted the presentation, which often includes seizures or altered level of consciousness after a febrile illness,² and discussed differential diagnosis, which includes metabolic disorder, febrile seizures, acute disseminated encephalomyelitis, meningitis, and encephalitis (autoimmune *vs* infectious). We also emphasised the important components of treatment for acute necrotising encephalitis with early steroids and IL-6 blockade, and other immunomodulatory treatments including intravenous immunoglobulin and plasma exchange.² Finally, we highlighted the high mortality rate of this diagnosis and poor prognosis for recovery in those who do survive.³

Malaria-Mücke bedroht Städte



Etwa 600.000 Menschen sterben jährlich an Malaria, die meisten von ihnen in ländlichen Gebieten. Doch nun bedroht eine invasive Mückenart auch die Städte.

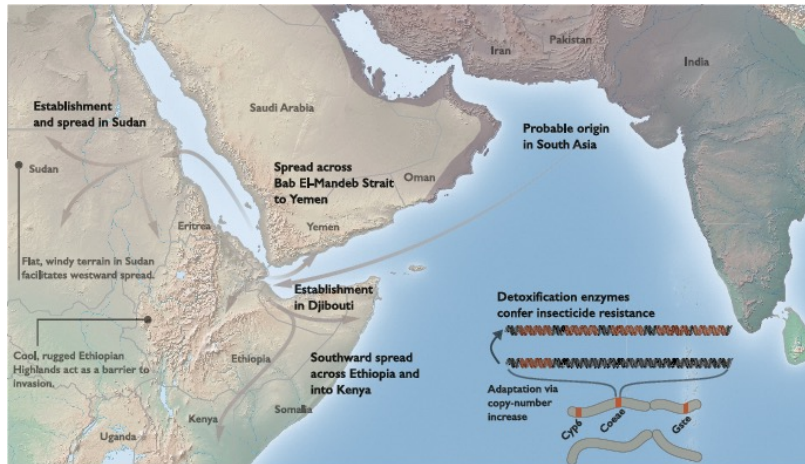


The origin, history, and resistance architecture of an invasive urban malaria mosquito in Africa

INTRODUCTION: In 2024, malaria resulted in more than 250 million cases and 550,000 deaths in Africa. Rural areas are typically most affected, especially during rainy seasons that provide abundant breeding sites for *Anopheles* mosquito vectors. First detected in Djibouti City in 2012, the invasion of Africa by the Asian malaria mosquito *Anopheles stephensi* has the potential to change the spatial and temporal distribution of malaria in Africa, undermining decades of malaria control progress. *An. stephensi* thrives in urban environments, where its populations are often less restricted by dry seasons. Now detected across the Horn of Africa, Kenya, and Yemen, and with sporadic reports in West Africa, *An. stephensi* has been associated with surges in malaria in Djibouti and Ethiopia, and modeling indicates an elevated threat to 126 million city dwellers across Africa. Control methods targeting native African *Anopheles* vectors appear poorly suited to *An. stephensi*, owing to variant population dynamics and behavior, as well as widespread insecticide resistance.

RATIONALE: The origin and number of invasion events by *An. stephensi* into Africa and routes of subsequent expansion are currently unknown, with previous genetic sampling unable to discriminate among competing hypotheses. Additionally, resistance mechanisms in the invasive range do not appear to involve common and readily detected mutations in insecticide target sites. Genomewide data are needed to reconstruct invasion routes, population structure, demographic history, and introduction timing, as well as the genomic architecture of insecticide resistance.

RESULTS: Genome sequencing of 645 *An. stephensi* samples from the invasive range in East Africa and the native range in Asia and the Middle East reveals that invasive *An. stephensi* are most closely related to samples from Afghanistan and Pakistan. Three distinct invasion fronts—Sudan, Ethiopia-Kenya, and Yemen—predominantly derive from the same initially introduced population, with Djibouti the likely primary bridgehead. Sudanese and Ethiopian-Kenyan incursions show signs of isolation by distance, with diversity declining with distance from Port Sudan and Port of Djibouti respectively, which is consistent with serial founder events and stepwise spread after maritime introduction. Population size reconstructions show bottlenecks that are broadly consistent with discovery dates. Landscape genetic analysis identifies the Ethiopian Highlands as a major barrier to gene flow, explaining slower and more restricted spread in Ethiopia-Kenya compared with rapid homogeneous spread across Sudan's flatter terrain. Selection scans and haplotype clustering reveal strong selection at detoxification gene families across both native and invasive ranges. Extensive and uniform copy-number variation (CNV) in the invasive range, as well as haplotype sharing, indicate that resistance was introduced from Asia.



The invasion of Africa by *An. stephensi*. Whole-genome sequence analysis revealed that invasive *An. stephensi* likely originated in South Asia. The initial bridgehead population in Djibouti seeded incursions into Sudan, Yemen, and through Ethiopia across the Horn of Africa and into Kenya. Contrasting rates of spread in Sudan and Ethiopia are underlain by different landscape types. Insecticide resistance in invasive populations is conferred by CNV at detoxification resistance genes, introduced from Asia.

CONCLUSION: The *An. stephensi* invasion originated in Asia, most likely in coastal Pakistan or northern India through maritime introduction in Djibouti. This seeded subsequent invasions, which is consistent with the history of discovery. The open Sahel west of Sudan is a high-risk corridor for ongoing expansion, and whether detections in West Africa represent contiguous spread is an urgent question. An accompanying data and analytical toolkit, released by the MalariaGEN consortium, will support real-time genomic surveillance, monitoring, and intervention design across the invasive range.

The deep-fried contradiction of MAHA Mondays at the Great American State Fair



Mondays at the Great American State Fair have been devoted to programming for the Make America Healthy Again movement. For two weeks, speakers on MAHA Mondays tried to shed light on why America is so sick and obese. They pointed fingers at food industry lobbyists, the health care system, social media, government regulations, lax government oversight and much more.

Never once, though, did they look around and suggest that part of the problem could be observed right at this very fair on the National Mall. Old-fashioned American entrepreneurship has created a landscape full of junk-food temptations — not to mention people who want to save you from them — and as the experts will tell you, the temptations usually win out. You could find plenty of evidence at the fair itself: There were more people standing in line for snacks and burgers than listening to these talking heads.



One of the first MAHA events June 29 even celebrated overindulgence. It was a pancake-eating contest, in which organizers struggled to find enough participants. They apparently drafted a few folks. One was Tucker Stewart, a senior adviser in the Agriculture Department, who survived a minor scandal last year when a sexually explicit novella that he wrote while working for a senator resurfaced on Capitol Hill.

The contestants had to chow down a five-pancake stack, drizzled with a sweetened sauce fashioned from mascarpone, cream cheese, milk, sugar “and Judy’s love,” said Judy Wang, founder and proprietor of Judy’s Family Cafe in Galesburg, Illinois.



One significant difference is that the new guidelines encourage more meat and full-fat dairy consumption — recommendations that may have been pushed by authors with ties to beef, dairy and pork industry groups, according to the Physicians Committee for Responsible Medicine. Means made no mention of this in his talk.

Means frequently talked as if he needed a bogeyman around which to rally adherents to the MAHA cause. You only had to attend two MAHA Mondays to realize that there are a lot of bogeymen in this world, some more real than others.