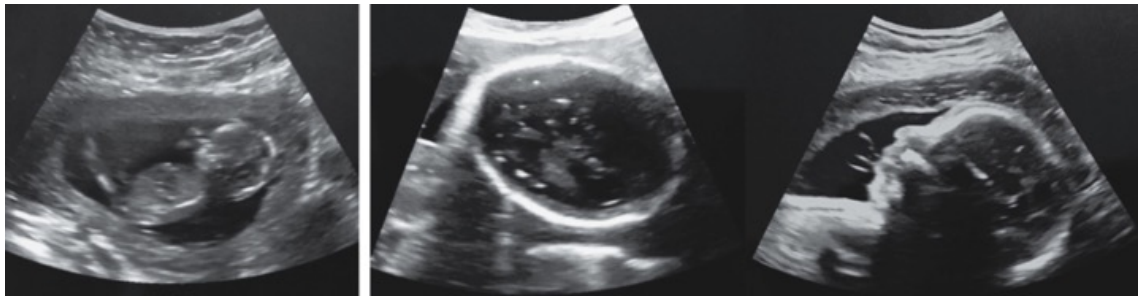
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



A 6-month-old baby boy was referred to a pediatric neurology clinic in Brazil for evaluation of developmental delay. At the beginning of the second trimester, the baby's mother had had a rash. At birth, the baby had microcephaly. He subsequently developed severe developmental delay and epilepsy. Prenatal ultrasonography at 12 weeks' gestation and at 29 weeks' gestation are shown. What is the underlying etiology?

Congenital cytomegalovirus

Congenital toxoplasmosis

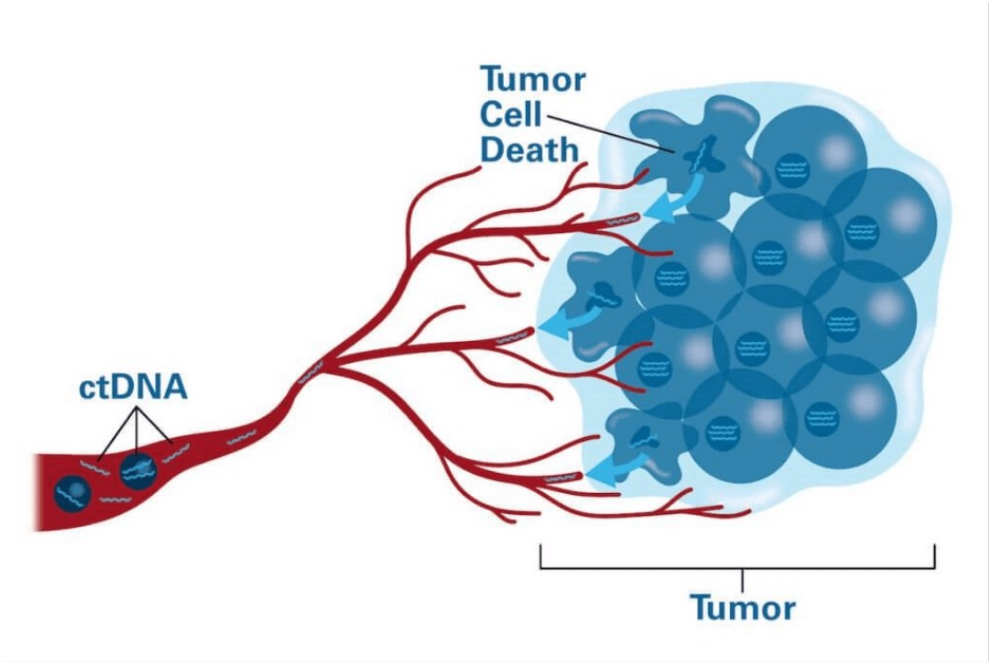
Congenital Zika syndrome

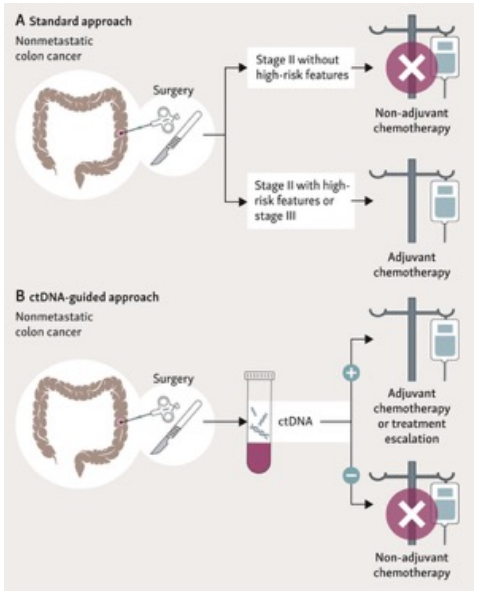
Inborn error of metabolism

In utero toxin exposure

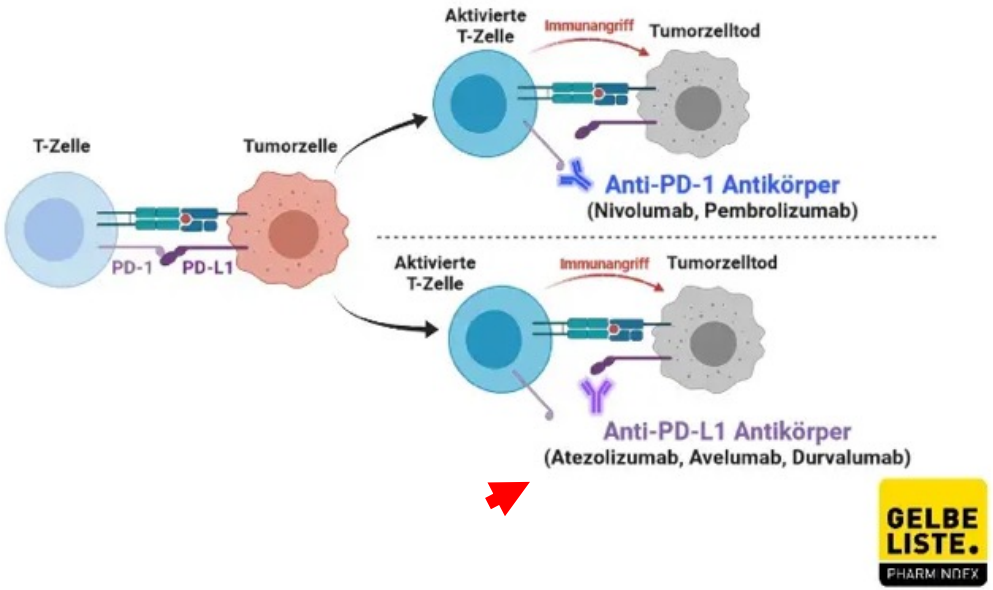
A diagnosis of probable congenital Zika syndrome was made. The baby's mother had tested positive for Zika virus while pregnancy during the 2015-2016 Zika virus epidemic. At birth, the baby had a positive serum IgM test for Zika virus. Physical, occupational, and speech therapy was recommended.

ctDNA-guided treatment means using circulating tumor DNA (ctDNA) from a blood test (liquid biopsy) to personalize and manage cancer therapy, helping doctors decide if, when, and what treatment (like chemo, immunotherapy) a patient needs, especially after surgery, by finding microscopic cancer (minimal residual disease or MRD) and tracking treatment response, reducing overtreatment while catching recurrence early.





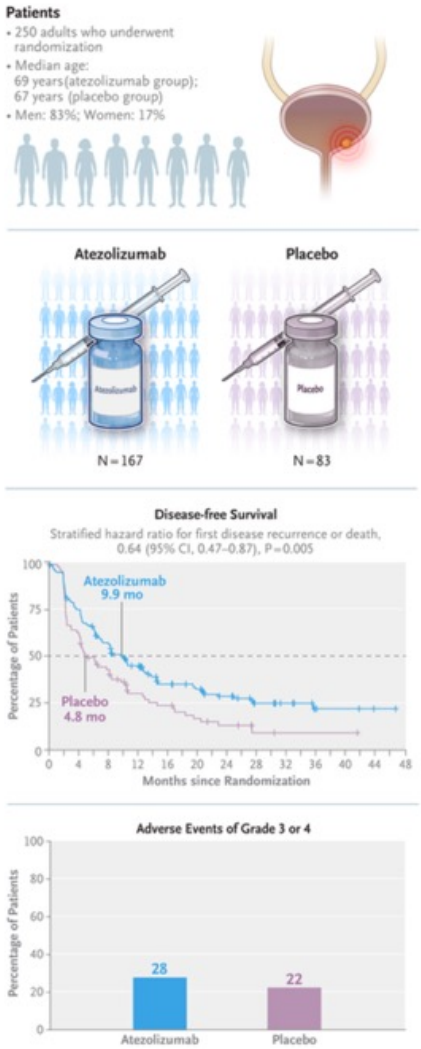
Atezolizumab (Handelsname Tecentriq) ist ein monoklonaler Antikörper, der als Immuntherapie Krebs bekämpft, indem er das Protein PD-L1 blockiert, welches Tumorzellen nutzen, um Immunzellen abzuschalten. Es wird bei verschiedenen Krebsarten eingesetzt, darunter nicht-kleinzelliges Lungenkarzinom (NSCLC), kleinzelliges Lungenkarzinom (SCLC) und Leberzellkarzinom (HCC). Die Verabreichung erfolgt als Infusion oder, neuerdings, als subkutane Injektion (Tecentriq Hybreza), um die körpereigene Immunabwehr gegen den Krebs zu stärken.



ctDNA-Guided Adjuvant Atezolizumab in Muscle-Invasive Bladder Cancer

Patients with muscle-invasive bladder cancer have varied outcomes after cystectomy. Circulating tumor DNA (ctDNA)–based detection of molecular residual disease may identify patients at high risk for recurrence after cystectomy who can benefit from adjuvant immunotherapy, thus sparing patients at lower risk from unnecessary treatment burden.

In a phase 3, double-blind, randomized trial, we used serial ctDNA testing to monitor (for up to 1 year) patients with muscle-invasive bladder cancer and no radiographic evidence of disease after surgery. Eligible patients who tested ctDNA-positive during surveillance were randomly assigned in a 2:1 ratio to receive intravenous atezolizumab or placebo every 4 weeks for up to 1 year. The primary end point was investigator-assessed disease-free survival. Overall survival was a secondary end point that was assessed in a hierarchical fashion to control for alpha. Patients who persistently tested ctDNA-negative did not receive atezolizumab or placebo.



Muscle-invasive bladder cancer is an aggressive disease that is typically treated with radical cystectomy, with or without neoadjuvant therapy. These interventions are curative for many patients; however, disease recurrence, which is associated with poor prognosis and unfavorable survival, will develop in approximately 50% of patients. Hence, adjuvant immunotherapy is recommended, but data showing a significant survival advantage with this approach are lacking. Given patients' varied outcomes after cystectomy, a goal is to differentiate patients with occult residual disease in whom additional treatment is recommended from those in whom the burden of unnecessary therapy can be safely avoided. Circulating tumor DNA (ctDNA)–based detection of molecular residual disease is a prognostic biomarker in several cancers and has been used to determine which patients are likely to benefit from adjuvant chemotherapy in colon cancer. In muscle-invasive bladder cancer, growing evidence suggests that ctDNA testing also may aid in informing decisions about adjuvant treatment. Exploratory data and single-group studies have shown that ctDNA status is strongly prognostic after cystectomy. In addition, the benefit of adjuvant immunotherapy may be restricted to patients with ctDNA-positive status. However, data from prospective randomized trials in muscle-invasive bladder cancer are lacking, although they are necessary in order to change global practice. Therefore, the use of ctDNA analysis in muscle-invasive bladder cancer remains exploratory.

Patients

Patients with muscle-invasive bladder cancer were eligible for the surveillance phase if they were at least 18 years of age, had an Eastern Cooperative Oncology Group performance-status score of 2 or less (on a scale from 0 to 5, with higher scores indicating greater disability), had (y)pT2–4aN0M0 or (y)pT0–4aN+M0 surgical staging, were disease-free as assessed radiographically by the investigator, and were enrolled 6 to 24 weeks after cystectomy.

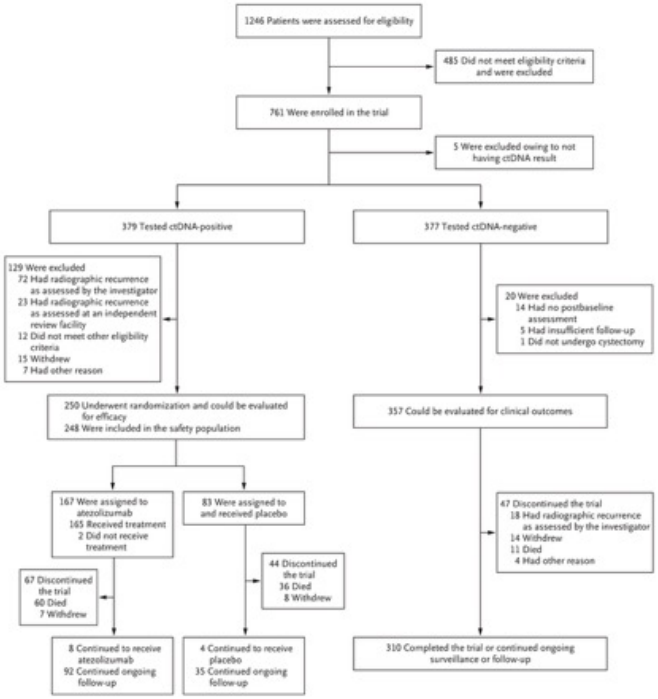
Patients with a ctDNA-positive test result at any time during surveillance who remained disease-free as assessed radiographically by the investigator (confirmed at an independent review facility) and met the eligibility criteria for the treatment phase underwent randomization.

Trial Design and Treatment

During the surveillance phase, serial ctDNA monitoring was conducted in patients outside mainland China with the Signatera molecular residual disease test and in patients in mainland China with molecular residual disease testing from Tianjin Medical Laboratory, BGI; tests were purchased at full cost.

End Points

The primary end point was investigator-assessed disease-free survival, defined as the time from randomization to the first recurrence (local, urinary tract, or distant metastasis of urothelial carcinoma) or death from any cause.



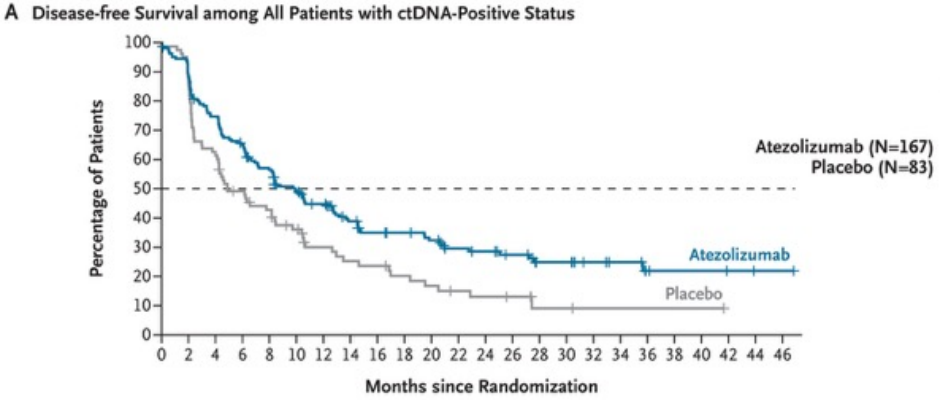
Testing, Randomization, and Follow-up of Patients in the Trial.

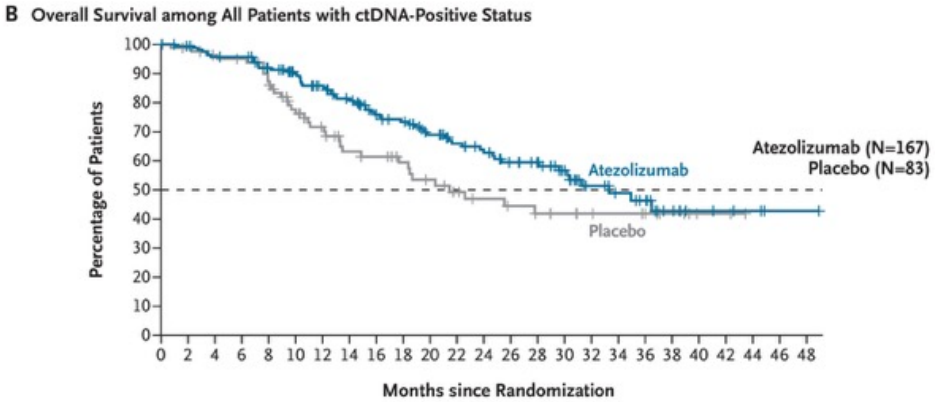
Eligible patients were enrolled in a surveillance phase during which they received serial monitoring of circulating tumor DNA (ctDNA) for 1 year after cystectomy. Patients were grouped according to final ctDNA status at the end of the surveillance monitoring period. If patients tested positive at any point, they were screened for entry into the treatment phase. Patients who met eligibility criteria were randomly assigned to receive atezolizumab or placebo (efficacy population). Patients who had persistent ctDNA-negative status through the end of the ctDNA monitoring period were followed for disease-free survival and overall survival. Patients were considered to have persistent ctDNA-negative status if they had at least one negative test result and no positive test result. To be included in the population of patients with persistent ctDNA-negative status who could be evaluated for clinical outcomes (exploratory analysis), patients must have had at least one postbaseline clinical outcome assessment and have completed 1 year of surveillance or discontinued from surveillance without a ctDNA-positive result.

Characteristic	ctDNA-Positive Status		Persistent ctDNA-Negative Status
	Atezolizumab (N=167)	Placebo (N=83)	No Atezolizumab or Placebo (N=357)
Age			
Median (range) — yr	69 (42–87)	67 (44–84)	69 (36–90)
≥65 yr	117 (70)	48 (58)	246 (69)
Male sex — no. (%)	141 (84)	67 (81)	278 (78)
Race or ethnic group — no. (%)†			
White	104 (62)	50 (60)	186 (52)
Asian	52 (31)	27 (33)	137 (38)
American Indian or Alaska Native	4 (2)	0	5 (1)
Black	0	2 (2)	7 (2)
Native Hawaiian or other Pacific Islander	0	0	2 (1)
Unknown or multiple	7 (4)	4 (5)	20 (6)
Hispanic ethnic group — no. (%)†			
Yes	19 (11)	9 (11)	31 (9)
No	141 (84)	70 (84)	308 (86)
Not stated or unknown	7 (4)	4 (5)	18 (5)
Geographic region — no. (%)			
Asia Pacific	51 (31)	27 (33)	137 (38)
Central and South America	14 (8)	6 (7)	25 (7)
Europe	101 (60)	49 (59)	191 (54)
North America	1 (1)	1 (1)	4 (1)
ECOG performance-status score — no./total no. (%)‡			
0	113/167 (68)	53/83 (64)	232/353 (66)
1	52/167 (31)	29/83 (35)	110/353 (31)
2	2/167 (1)	1/83 (1)	11/353 (3)
PD-L1 status — no./total no. (%)§			
IC0 or IC1	108/167 (65)	53/83 (64)	189/356 (53)
IC2 or IC3	59/167 (35)	30/83 (36)	167/356 (47)
Histologic variants present — no. (%)	18 (11)	8 (10)	56 (16)
Previous neoadjuvant chemotherapy — no. (%)			
Yes	80 (48)	33 (40)	168 (47)
No	87 (52)	50 (60)	189 (53)
Tumor stage after cystectomy — no./total no. (%)			
≤T2	46/167 (28)	24/83 (29)	166/355 (47)
T3 or T4	121/167 (72)	59/83 (71)	189/355 (53)
Nodal status — no. (%)			
Negative	71 (43)	35 (42)	285 (80)
Positive	96 (57)	48 (58)	72 (20)
No. of lymph nodes removed — no./total no. (%)			
<10	44/166 (27)	16/79 (20)	85/349 (24)
≥10	122/166 (73)	63/79 (80)	264/349 (76)
Pathological staging at cystectomy — no./total no. (%)			
pT2N0	8/167 (5)	3/82 (4)	62/355 (17)
ypT2N0	15/167 (9)	5/82 (6)	61/355 (17)
(y)pT2N+	30/167 (18)	18/82 (22)	43/355 (12)
(y)pT3–4N0	49/167 (29)	26/82 (32)	160/355 (45)
(y)pT3–4N+	65/167 (39)	30/82 (37)	29/355 (8)
Time from cystectomy to first ctDNA-positive sample — no. (%)			
≤20 wk	117 (70)	59 (71)	NA
>20 wk	50 (30)	24 (29)	NA
ctDNA-positive status — no. (%)			
At initial test	99 (59)	49 (59)	NA
At subsequent tests	68 (41)	34 (41)	NA

Safety Summary.

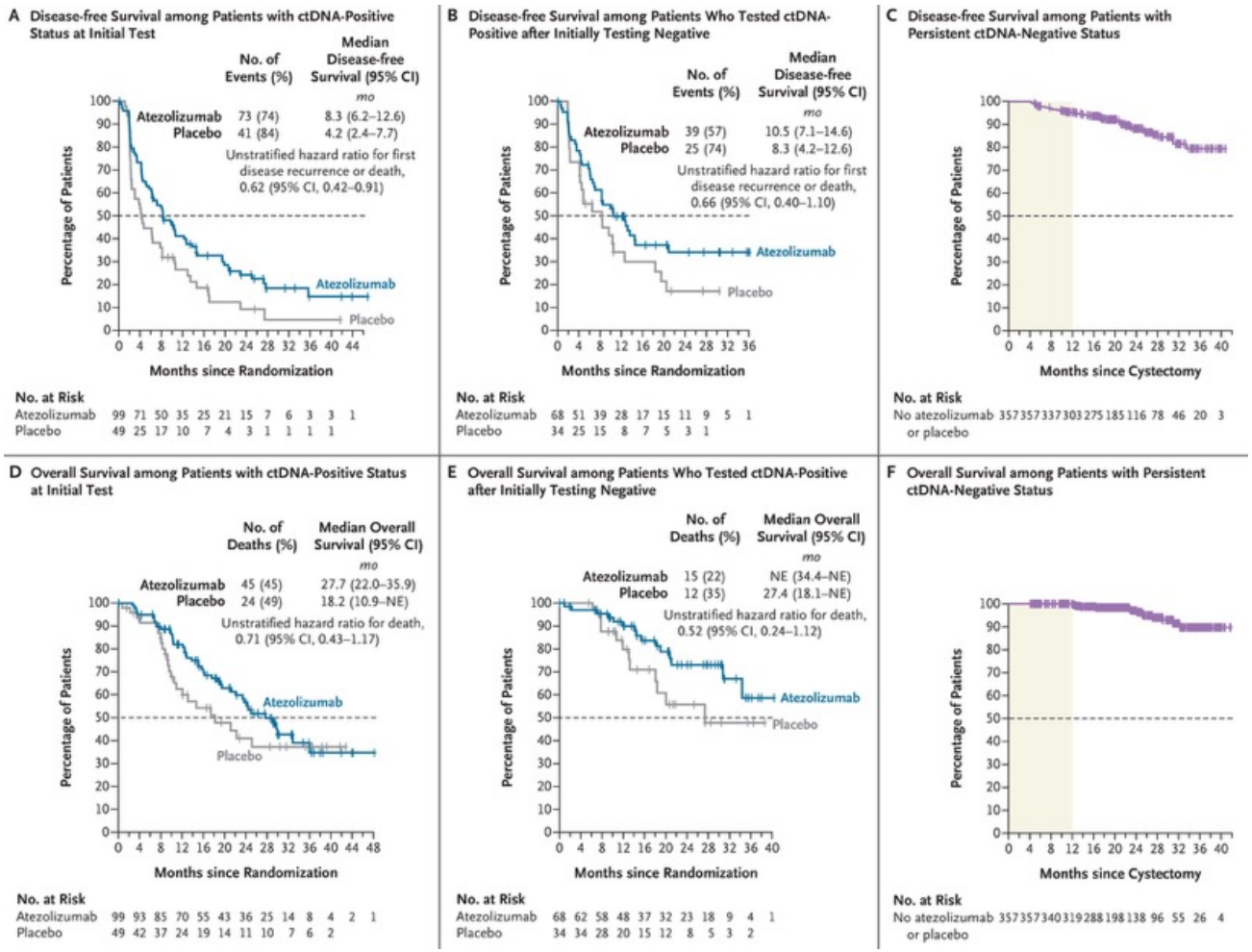
Event	Atezolizumab (N=165)	Placebo (N=83)
	number (percent)	
Adverse event of any grade	138 (84)	71 (86)
Any-grade adverse event related to atezolizumab or placebo	81 (49)	42 (51)
Grade 3 or 4 adverse event	47 (28)	18 (22)
Grade 3 or 4 adverse event related to atezolizumab or placebo	12 (7)	3 (4)
Death due to adverse event	5 (3)	2 (2)
Death due to adverse event related to atezolizumab or placebo	3 (2)†	0
Serious adverse event	44 (27)	17 (20)
Serious adverse event related to atezolizumab or placebo	9 (5)	0
Adverse event leading to discontinuation of atezolizumab or placebo	15 (9)	3 (4)
Adverse event leading to interruption of atezolizumab or placebo	39 (24)	16 (19)
Immune-mediated adverse event	64 (39)	10 (12)
Grade 3 or 4 immune-mediated adverse event	8 (5)	1 (1)
Death due to immune-mediated adverse event	1 (1)	0





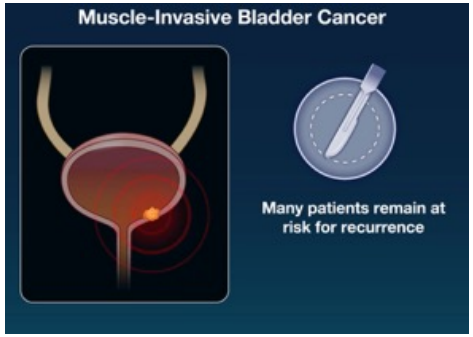
Disease-free Survival and Overall Survival.

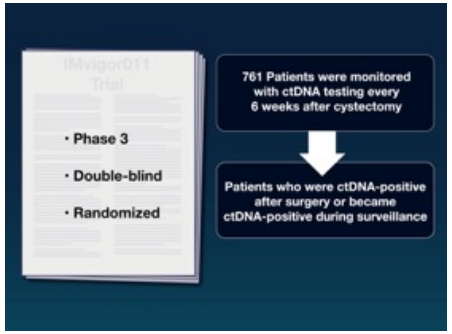
Panel A shows investigator-assessed disease-free survival among all patients with ctDNA-positive status who underwent randomization (primary end point). Panel B shows overall survival in the same population (secondary end point). In both panels, tick marks indicate censored data. NE denotes could not be evaluated.



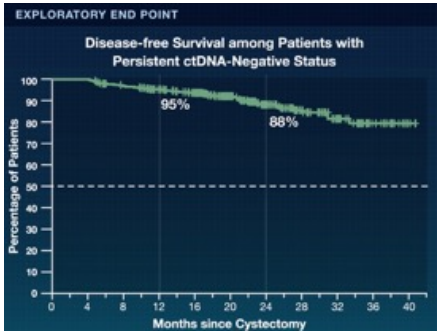
Disease-free Survival and Overall Survival in Exploratory Populations.

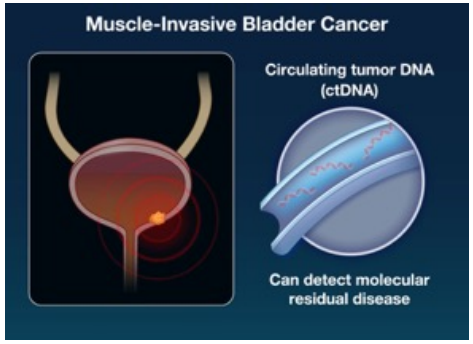
Panel A shows investigator-assessed disease-free survival among patients with ctDNA-positive status at the initial test. Panel B shows investigator-assessed disease-free survival among patients who tested ctDNA-positive after initially testing negative. Panel C shows investigator-assessed disease-free survival among patients with persistent ctDNA-negative status (exploratory end point). Panels D, E, and F show overall survival in the same populations. In Panels C and F, shading indicates the duration of the surveillance period for ctDNA monitoring. In the analysis of overall survival among patients with persistent ctDNA-negative status (exploratory end point; Panel F), 15 ctDNA-negative patients (4%) who had disease recurrence during the ctDNA monitoring period were discontinued from the trial and therefore had their data censored for the analysis. In Panels A, B, D, and E, the time at zero corresponds to the date of randomization, whereas in Panels C and F, the time at zero corresponds to the date of cystectomy. In all panels, tick marks indicate censored data.

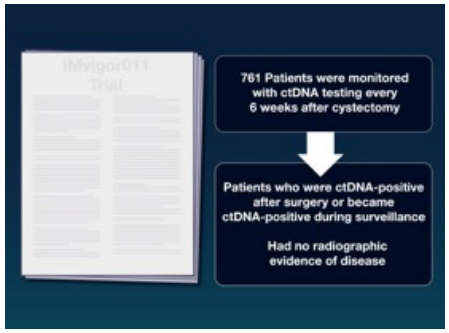

Muscle-Invasive Bladder Cancer
Many patients remain at risk for recurrence

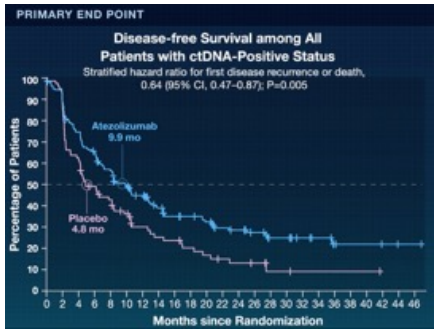

IMvigor011 Trial
• Phase 3
• Double-blind
• Randomized
761 Patients were monitored with ctDNA testing every 6 weeks after cystectomy
Patients who were ctDNA-positive after surgery or became ctDNA-positive during surveillance

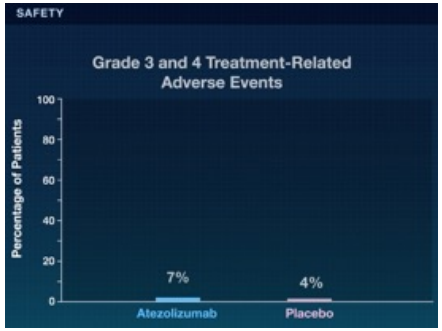

Patients who remained ctDNA-negative were observed without adjuvant treatment

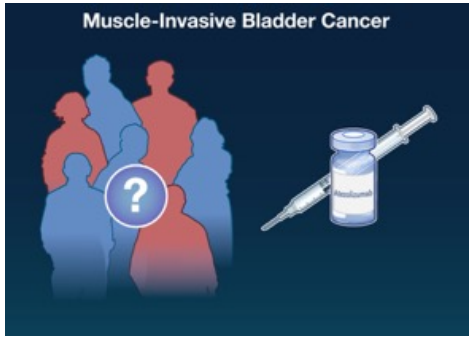

EXPLORATORY END POINT
Disease-free Survival among Patients with Persistent ctDNA-Negative Status
95%
88%
Percentage of Patients
Months since Cystectomy


Muscle-Invasive Bladder Cancer
Circulating tumor DNA (ctDNA)
Can detect molecular residual disease

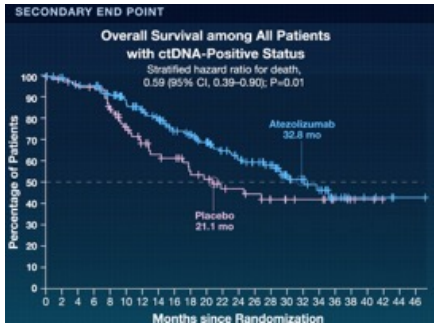

IMvigor011 Trial
761 Patients were monitored with ctDNA testing every 6 weeks after cystectomy
Patients who were ctDNA-positive after surgery or became ctDNA-positive during surveillance
Had no radiographic evidence of disease


PRIMARY END POINT
Disease-free Survival among All Patients with ctDNA-Positive Status
Stratified hazard ratio for first disease recurrence or death, 0.64 (95% CI, 0.47–0.87); P=0.005
Atezolizumab 9.9 mo
Placebo 4.8 mo
Percentage of Patients
Months since Randomization


SAFETY
Grade 3 and 4 Treatment-Related Adverse Events
Percentage of Patients
7%
4%
Atezolizumab
Placebo


Muscle-Invasive Bladder Cancer
?


Atezolizumab
Placebo
N=167
N=83
Every 4 weeks for up to 1 year

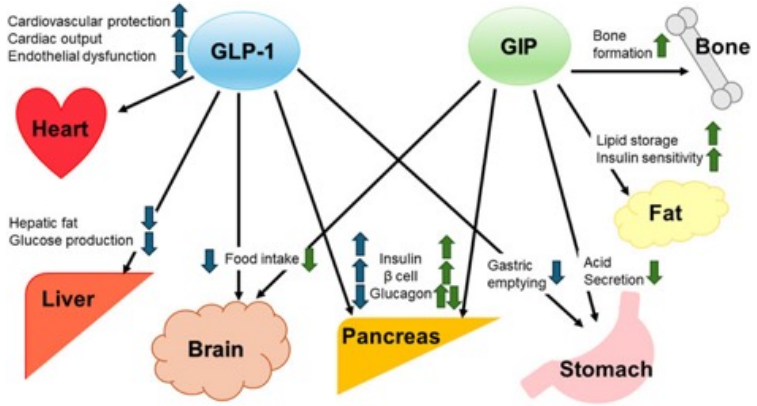

SECONDARY END POINT
Overall Survival among All Patients with ctDNA-Positive Status
Stratified hazard ratio for death, 0.59 (95% CI, 0.39–0.90); P=0.01
Atezolizumab 32.8 mo
Placebo 21.1 mo
Percentage of Patients
Months since Randomization


ctDNA-guided adjuvant therapy with atezolizumab led to significantly longer disease-free and overall survival

Dulaglutid ist ein GLP-1-Rezeptoragonist, ein Medikament zur Behandlung von Typ-2-Diabetes, das den Blutzuckerspiegel durch Nachahmung des natürlichen Hormons GLP-1 senkt, indem es die Insulinproduktion bei Bedarf steigert, die Glukosefreisetzung der Leber hemmt und die Magenentleerung verlangsamt. Es wird einmal wöchentlich als subkutane Injektion verabreicht und hilft auch, das Sättigungsgefühl zu erhöhen und das Risiko für Herz-Kreislauf-Erkrankungen zu senken.

Tirzepatid ist ein neuartiger dualer GIP/GLP-1-Rezeptoragonist, ein injizierbarer Wirkstoff zur Behandlung von Typ-2-Diabetes und Adipositas (starkes Übergewicht), der Blutzucker senkt und das Hungergefühl reduziert, indem er körpereigene Hormone nachahmt. Es wird einmal wöchentlich selbst gespritzt und hilft bei der Gewichtsabnahme sowie bei Adipositas-bedingter Schlafapnoe. Die häufigsten Nebenwirkungen sind Magen-Darm-Beschwerden wie Übelkeit, Durchfall und Erbrechen.

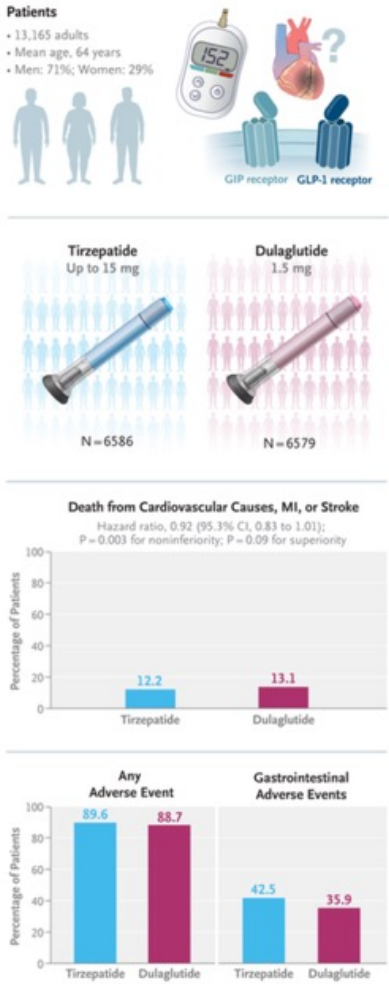
glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors,



Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes

Tirzepatide, a dual incretin agonist of the glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors, has favorable effects on glycemic control and body weight. The effects on cardiovascular outcomes are uncertain.

We conducted an active-comparator–controlled, double-blind, noninferiority trial in which patients with type 2 diabetes and atherosclerotic cardiovascular disease were randomly assigned in a 1:1 ratio to receive a weekly subcutaneous injection of tirzepatide (up to 15 mg) or dulaglutide (1.5 mg), an agent that has been shown to reduce the incidence of cardiovascular events. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke and was tested for noninferiority of tirzepatide to dulaglutide with a margin of 1.05 for the upper limit of the 95.3% confidence interval for the hazard ratio. An upper limit of less than 1.00 was considered to indicate superiority of tirzepatide to dulaglutide.



Tirzepatide is a dual agonist of the GLP-1 and glucose-dependent insulinotropic polypeptide receptors. Clinical trials have shown that tirzepatide leads to incremental benefits with respect to glycemic control, weight, atherogenic lipoprotein levels, blood pressure, and kidney-related outcomes as compared with selective GLP-1 receptor agonists or other glucose-lowering agents. These benefits, if sustained over time, could also have incremental effects on the incidence of atherosclerotic events. However, data from a randomized, clinical trial of the effect of tirzepatide on cardiovascular outcomes have been lacking.

The established role of GLP-1 receptor agonists in the management of type 2 diabetes in patients with high cardiovascular risk precluded direct comparison of tirzepatide with a placebo control in a large, long-term clinical trial. We conducted the Study of Tirzepatide Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes (SURPASS-CVOT) to determine the cardiovascular effects of tirzepatide as compared with those of the selective GLP-1 receptor agonist dulaglutide in patients with type 2 diabetes and established atherosclerotic cardiovascular disease. Because dulaglutide has been shown to reduce the incidence of cardiovascular events as compared with placebo, we sought to determine whether tirzepatide was noninferior to dulaglutide with respect to cardiovascular events, as well as whether tirzepatide was associated with a greater cardiovascular benefit.

Patients at least 40 years of age were eligible if they had type 2 diabetes with a glycated hemoglobin level between 7.0% (53 mmol per mole) and 10.5% (91 mmol per mole), a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 25, and established atherosclerotic cardiovascular disease in at least one vascular territory. Among the exclusion criteria were any cardiovascular event in the 60 days before screening, use of a GLP-1 receptor agonist or pramlintide in the 3 months before screening, planned treatment for diabetic retinopathy or macular edema, chronic advanced heart failure, a history of pancreatitis, a clinically significant abnormality in gastric emptying or previous bariatric surgery, active liver disease (not including metabolic dysfunction–associated steatohepatitis), an estimated glomerular filtration rate (eGFR) of less than 15 ml per minute per 1.73 m^2 of body-surface area or use of long-term dialysis, or a family or personal history of multiple endocrine neoplasia or medullary thyroid carcinoma.

Randomization and Trial Regimen

Eligible patients were randomly assigned in a 1:1 ratio to receive weekly subcutaneous injections of tirzepatide at a dose adjusted up to 15 mg or dulaglutide at a dose of 1.5 mg. Randomization was stratified according to country and the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors at baseline. Tirzepatide was initiated at a dose of 2.5 mg and increased by 2.5 mg every 4 weeks to a maximum of 15 mg or to the maximum tolerated dose. Because the dose of dulaglutide remained at 1.5 mg throughout the trial, a sham dose-escalation scheme was used to maintain trial blinding.

Trial End Points

The primary end point was a composite of MACE and others.

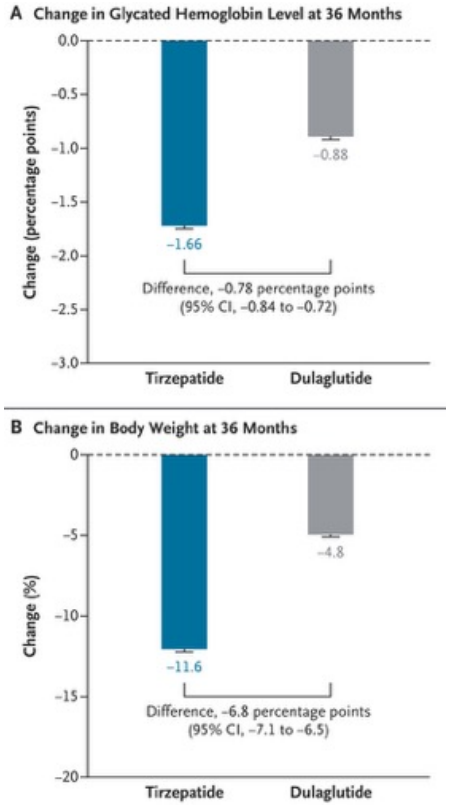
Characteristic	Tirzepatide (N=6586)	Dulaglutide (N=6579)
Age — yr	64.0±8.8	64.1±8.7
Female sex — no. (%)	1891 (28.7)	1926 (29.3)
White race — no./total no. (%)†	5299/6501 (81.5)	5282/6492 (81.4)
Hispanic or Latino ethnic group — no. (%)†	1988 (30.2)	1981 (30.1)
Geographic region — no. (%)		
North America	970 (14.7)	970 (14.7)
South America	1896 (28.8)	1897 (28.8)
Europe	3047 (46.3)	3034 (46.1)
Asia–Pacific	673 (10.2)	678 (10.3)
History of ASCVD — no. (%)		
Coronary artery disease	4286 (65.1)	4267 (64.9)
Myocardial infarction	3097 (47.0)	3119 (47.4)
Coronary revascularization	3756 (57.0)	3773 (57.3)
Stroke	1253 (19.0)	1272 (19.3)
Peripheral artery disease	1660 (25.2)	1674 (25.4)
Previous heart failure	1310 (19.9)	1368 (20.8)
Hypertension — no. (%)	5941 (90.2)	5932 (90.2)
Dyslipidemia — no. (%)	5685 (86.3)	5611 (85.3)
Current tobacco use — no. (%)	963 (14.6)	996 (15.1)
Duration of diabetes — yr	14.8±8.8	14.7±8.7
Cardiovascular risk factors		
Weight — kg	92.6±18.9	92.5±18.8
Body-mass index	32.6±5.5	32.6±5.5
Blood pressure		
Systolic — mm Hg	135.1±15.5	135.5±15.8
Diastolic — mm Hg	77.9±9.7	78.1±9.7
Glycated hemoglobin level — %	8.40±0.92	8.38±0.93
LDL cholesterol level — mg/dl	80.5±36.8	80.7±38.0
Median triglyceride level (IQR) — mg/dl	160.3 (116.0–225.9)	159.4 (116.0–224.1)
Estimated GFR		
Mean value — ml/min/1.73 m^2	78.5±24.2	79.2±23.5
Value of <60 ml/min/1.73 m^2 — no./total no. (%)	1516/6492 (23.4)	1412/6512 (21.7)
Urinary albumin-to-creatinine ratio (IQR)‡	22.0 (9.0–86.0)	22.0 (9.0–81.0)
Microalbuminuria — no./total no. (%)	2072/6472 (32.0)	2070/6482 (31.9)
Macroalbuminuria — no./total no. (%)	754/6472 (11.7)	737/6482 (11.4)

Primary and Key Secondary End Points.

End Point	Tirzepatide (N=6586)	Dulaglutide (N=6579)	Hazard Ratio (95% CI)	Difference (95% CI)
Primary end point				
Death from cardiovascular causes, myocardial infarction, or stroke — no. of patients with event (%)	801 (12.2)	862 (13.1)	0.92 (0.83 to 1.01)†	—
Key secondary end points				—
Death from cardiovascular causes — no. (%)	367 (5.6)	408 (6.2)	0.89 (0.77 to 1.02)	—
Myocardial infarction — no. (%)	311 (4.7)	357 (5.4)	0.86 (0.74 to 1.00)	—
Stroke — no. (%)	229 (3.5)	249 (3.8)	0.91 (0.76 to 1.09)	—
Death from cardiovascular causes, myocardial infarction, stroke, or coronary revascularization — no. (%)	1089 (16.5)	1217 (18.5)	0.88 (0.81 to 0.96)	—
Death from cardiovascular causes or hospitalization or urgent visit for heart failure — no. (%)	512 (7.8)	557 (8.5)	0.91 (0.81 to 1.03)	—
Death from any cause — no. (%)	566 (8.6)	669 (10.2)	0.84 (0.75 to 0.94)	—
Change in eGFR from baseline to 36 mo — ml/min/1.73 m^2‡	−5.72±0.44	−8.90±0.39	—	3.17 (2.09 to 4.26)
Change in metabolic risk factors§				
Glycated hemoglobin level				
Value at baseline (95% CI) — %	8.40 (8.38 to 8.43)	8.38 (8.36 to 8.40)	—	NA
Change at 36 mo (95% CI) — percentage points	−1.66 (−1.70 to −1.62)	−0.88 (−0.92 to −0.83)	—	−0.78 (−0.84 to −0.72)
Body weight				
Value at baseline (95% CI) — kg	92.6 (92.2 to 93.1)	92.5 (92.1 to 93.0)	—	NA
Change at 36 mo (95% CI) — %	−11.6 (−11.8 to −11.4)	−4.8 (−5.0 to −4.6)	—	−6.8 (−7.1 to −6.5)¶
Triglyceride level				
Value at baseline (95% CI) — mg/dl	166.2 (164.1 to 168.4)	165.2 (163.1 to 167.4)	—	NA
Change at 24 mo (95% CI) — %	−24.2 (−25.1 to −23.3)	−10.2 (−11.2 to −9.1)	—	−15.6 (−16.9 to −14.3)¶
Systolic blood pressure				
Value at baseline (95% CI) — mm Hg	134.8 (13.4 to 135.2)	135.3 (134.9 to 135.6)	—	NA
Change at 36 mo (95% CI) — mm Hg	−6.2 (−6.6 to −5.8)	−4.1 (−4.6 to −3.7)	—	−2.1 (−2.6 to −1.5)
LDL cholesterol level				
Value at baseline (95% CI) — mg/dl	72.2 (71.3 to 73.1)	72.1 (71.2 to 73.0)	—	NA
Change at 24 mo (95% CI) — %	−1.6 (−2.7 to −0.5)	−2.9 (−4.0 to −1.8)	—	1.3 (−0.2 to 2.8)¶

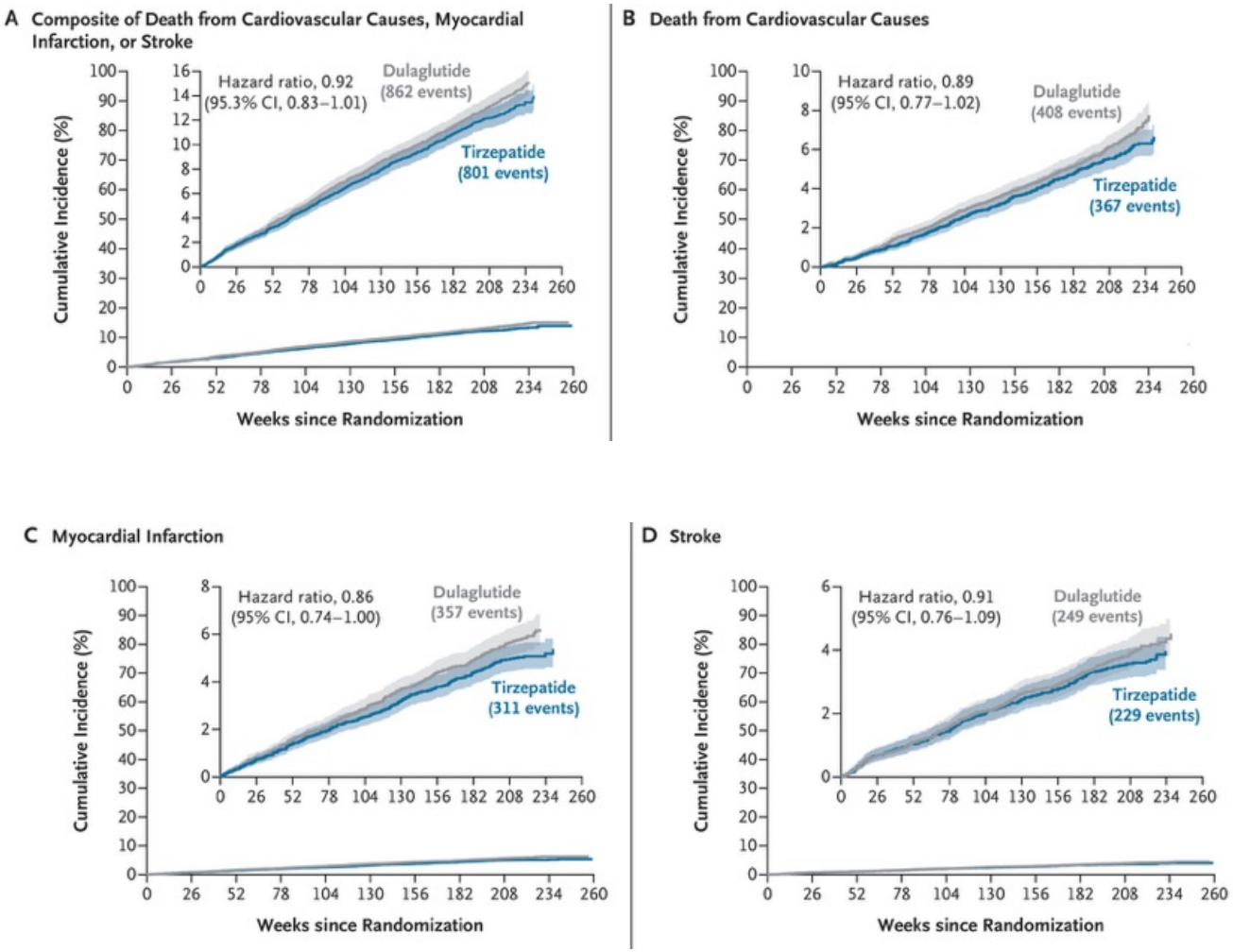
Adverse Events.

Event	Tirzepatide (N=6647)	Dulaglutide (N=6647)
	number of patients (percent)	
Any adverse event that emerged during treatment	5956 (89.6)	5894 (88.7)
Serious adverse event†	2117 (31.8)	2121 (31.9)
Adverse event leading to drug discontinuation	878 (13.2)	672 (10.1)
Prespecified adverse events of special interest		
Severe hypoglycemia	49 (0.7)	48 (0.7)
Gastrointestinal adverse event‡	2827 (42.5)	2387 (35.9)
Severe gastrointestinal adverse event	171 (2.6)	118 (1.8)
Nausea	1667 (25.1)	1486 (22.4)
Severe nausea	76 (1.1)	51 (0.8)
Vomiting	772 (11.6)	642 (9.7)
Severe vomiting	60 (0.9)	37 (0.6)
Diarrhea	1651 (24.8)	1267 (19.1)
Severe diarrhea	79 (1.2)	53 (0.8)
Pancreatic events		
Pancreatitis§	41 (0.6)	39 (0.6)
Pancreatic carcinoma¶	17 (0.3)	17 (0.3)
Gallbladder-related adverse events		
Cholelithiasis	158 (2.4)	134 (2.0)
Cholecystitis‖	91 (1.4)	84 (1.3)
Thyroid events		
Medullary thyroid cancer	2 (<0.1)	0
Other thyroid carcinoma	9 (0.1)	2 (<0.1)
Serious atrial fibrillation	59 (0.9)	58 (0.9)
Hypersensitivity reactions**		
Anaphylactic reaction	12 (0.2)	15 (0.2)
Hypersensitivity	377 (5.7)	330 (5.0)
Renal events		
Acute kidney injury	226 (3.4)	178 (2.7)
Chronic kidney disease	147 (2.2)	170 (2.6)



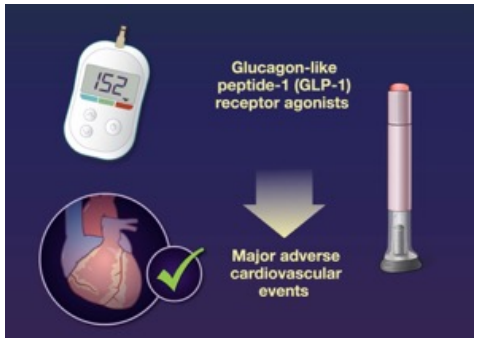
Changes in Glycated Hemoglobin Level and Body Weight over Time.

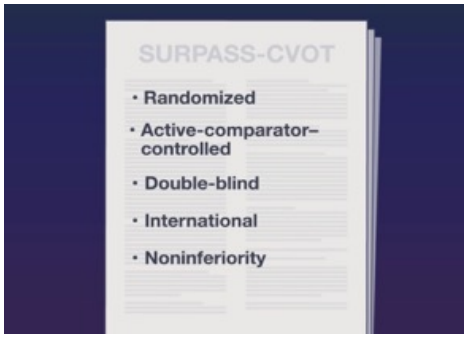
Panel A shows the change in the glycated hemoglobin level from baseline to 36 months in the tirzepatide group and the dulaglutide group. The mean glycated hemoglobin level in both groups at baseline was 8.4% (68 mmol per mole). Panel B shows the percent change in body weight in the two groups from baseline to 36 months. The mean body weight at baseline was 92.6 kg in the tirzepatide group and 92.5 kg in the dulaglutide group. Colored bars indicate least-squares means, and I bars indicate standard errors. Changes from baseline to the landmark time point were analyzed with an analysis of covariance model with treatment group, use of sodium–glucose cotransporter 2 inhibitors at baseline, country, and baseline value as covariates, with multiple imputation of missing values. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing.

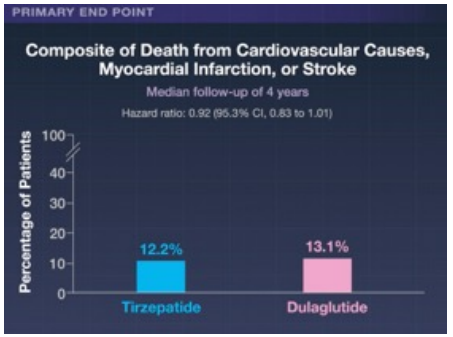


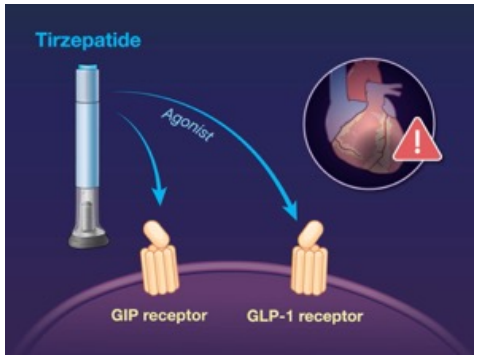
Cumulative Incidence of Cardiovascular Events (Primary and Key Secondary End Points).

Panel A shows the cumulative incidence of a composite of death from cardiovascular causes, myocardial infarction, or stroke (the primary efficacy end point). Panels B, C, and D show the cumulative incidence of the components of the primary end point. In each of the panels, the inset shows the same data on an enlarged y axis. Shading indicates 95% confidence intervals. Cumulative incidence was estimated with the Kaplan–Meier method. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing.

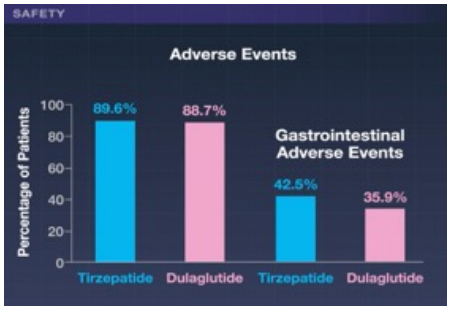

Glucagon-like peptide-1 (GLP-1) receptor agonists
Major adverse cardiovascular events

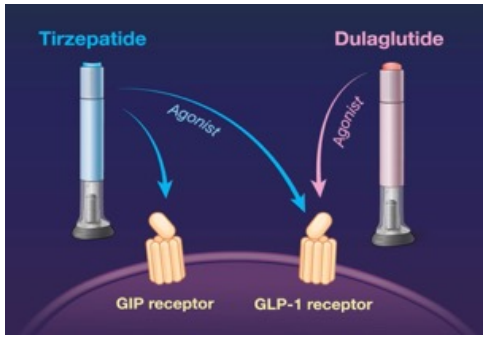

SURPASS-CVOT
• Randomized
• Active-comparator–controlled
• Double-blind
• International
• Noninferiority


PRIMARY END POINT
Composite of Death from Cardiovascular Causes, Myocardial Infarction, or Stroke
Median follow-up of 4 years
Hazard ratio: 0.92 (95.3% CI, 0.83 to 1.01)
Percentage of Patients
100
40
30
20
10
0
12.2%
13.1%
Tirzepatide
Dulaglutide

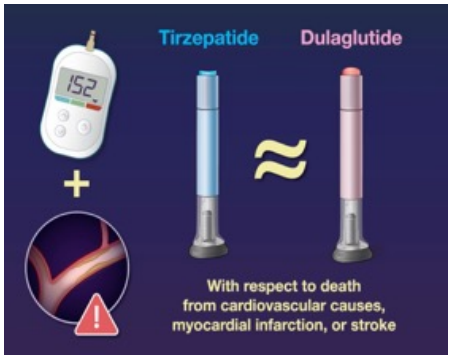

Tirzepatide
Agonist
GIP receptor
GLP-1 receptor


13,165 Patients ≥40 Years of Age
Type 2 Diabetes
Glycated Hemoglobin
7.0–10.5%
Overweight or Obesity
BMI ≥25
Atherosclerotic Cardiovascular Disease

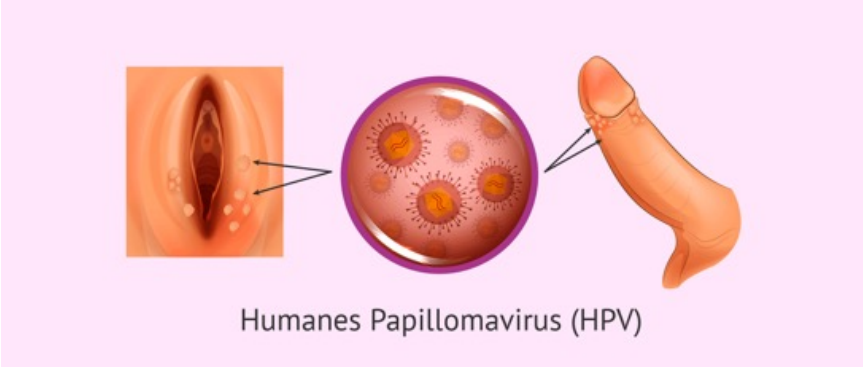

SAFETY
Adverse Events
Percentage of Patients
100
80
60
40
20
0
89.6%
88.7%
Gastrointestinal Adverse Events
42.5%
35.9%
Tirzepatide
Dulaglutide
Tirzepatide
Dulaglutide

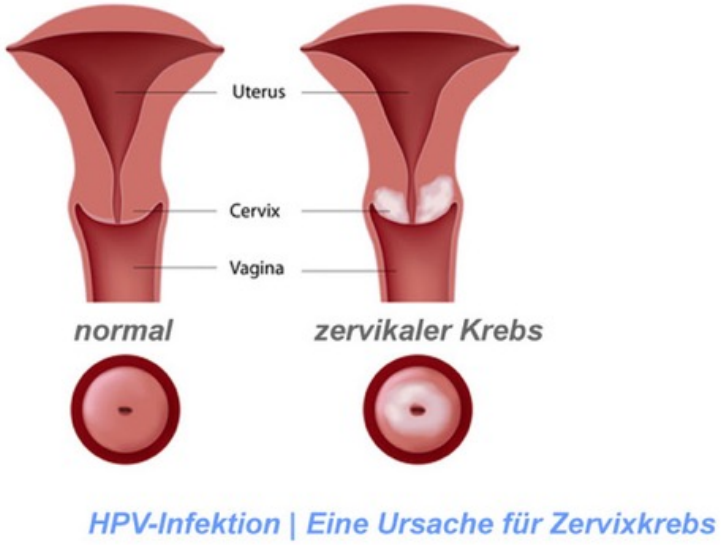

Tirzepatide
Dulaglutide
Agonist
Agonist
GIP receptor
GLP-1 receptor


Weekly subcutaneous injection
MONTH
Tirzepatide ≤15 mg
N=6586
Dulaglutide 1.5 mg
N=6579


Tirzepatide
Dulaglutide
With respect to death from cardiovascular causes, myocardial infarction, or stroke

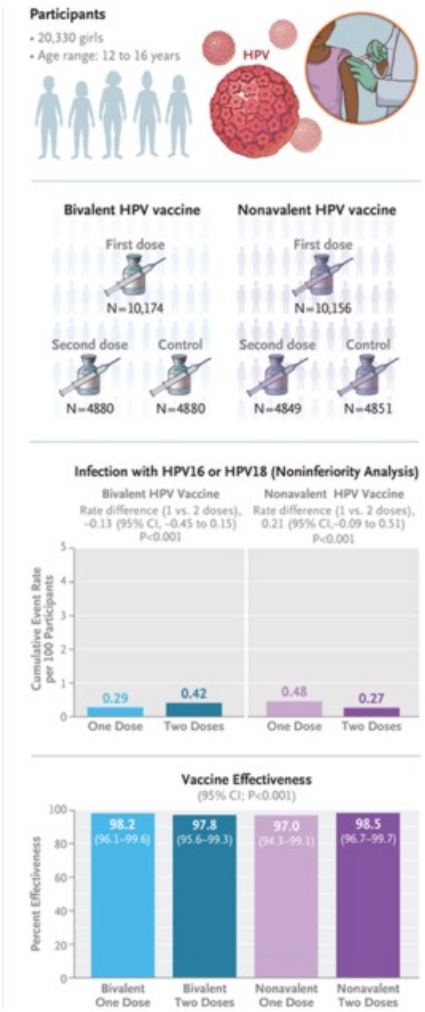
HPV (Humane Papillomaviren) sind sehr verbreitete Viren, die Haut- und Schleimhäute infizieren und meist harmlos sind, sich selbst heilen; jedoch können bestimmte Hochrisiko-Typen (z.B. 16, 18) Krebsvorstufen und Krebs verursachen, besonders Gebärmutterhalskrebs, während Niedrigrisiko-Typen (z.B. 6, 11) Feigwarzen auslösen. Übertragung erfolgt durch direkten Hautkontakt (Sex, Küssen), Schutz bietet die Impfung, die vor den gefährlichsten Typen schützt. Regelmäßige Vorsorgeuntersuchungen (Pap-Abstrich, HPV-Test) sind wichtig.





Noninferiority of One HPV Vaccine Dose to Two Doses

Multidose human papillomavirus (HPV) vaccination is efficacious, yet the vaccine has been underused globally. Emerging data suggest that a single dose may provide protection. Whether a single dose of HPV vaccine would provide similar protection to two doses is uncertain.
In this trial, we assessed whether one dose of an HPV vaccine was noninferior to two doses. Girls 12 to 16 years of age were randomly assigned, in a 1:1:1:1 ratio, to receive one or two doses of a bivalent HPV vaccine or one or two doses of a nonavalent HPV vaccine. The primary end point was new HPV type 16 or 18 infection occurring from month 12 to month 60 and persisting for at least 6 months. The prespecified noninferiority margin was 1.25 infections per 100 participants. We also assessed vaccine effectiveness by comparing HPV16 or HPV18 infection among the trial participants with that among girls and women enrolled in a nonrandomized survey.



In a post hoc analysis in the Costa Rica HPV Vaccine Trial, we found that protection against persistent HPV16 or HPV18 infection among women in a randomized population who received three doses of a bivalent vaccine was similar to that among women in a nonrandomized population who had received one dose, despite lower levels of antibodies among those who received one dose; the antibody levels in both groups remained protective a decade after vaccination. Additional nonrandomized data from India and a randomized, controlled efficacy trial in Kenya showed a high efficacy for a single dose of HPV vaccine. Sustained immune responses were observed in these studies, as well as in a trial conducted in Tanzania.

The double-blind, randomized, controlled ESCUDDO trial evaluated the noninferiority of one dose of a bivalent or nonavalent HPV vaccine to the respective two-dose regimens in the prevention of cervicovaginal HPV16 or HPV18 infection over a period of 5 years. The trial also used a survey of unvaccinated participants to assess vaccine effectiveness. The bivalent and nonavalent vaccines were chosen because they are approved by the Food and Drug Administration and prequalified by the WHO but differ in valency, adjuvant, and protection against different HPV types.

Procedures

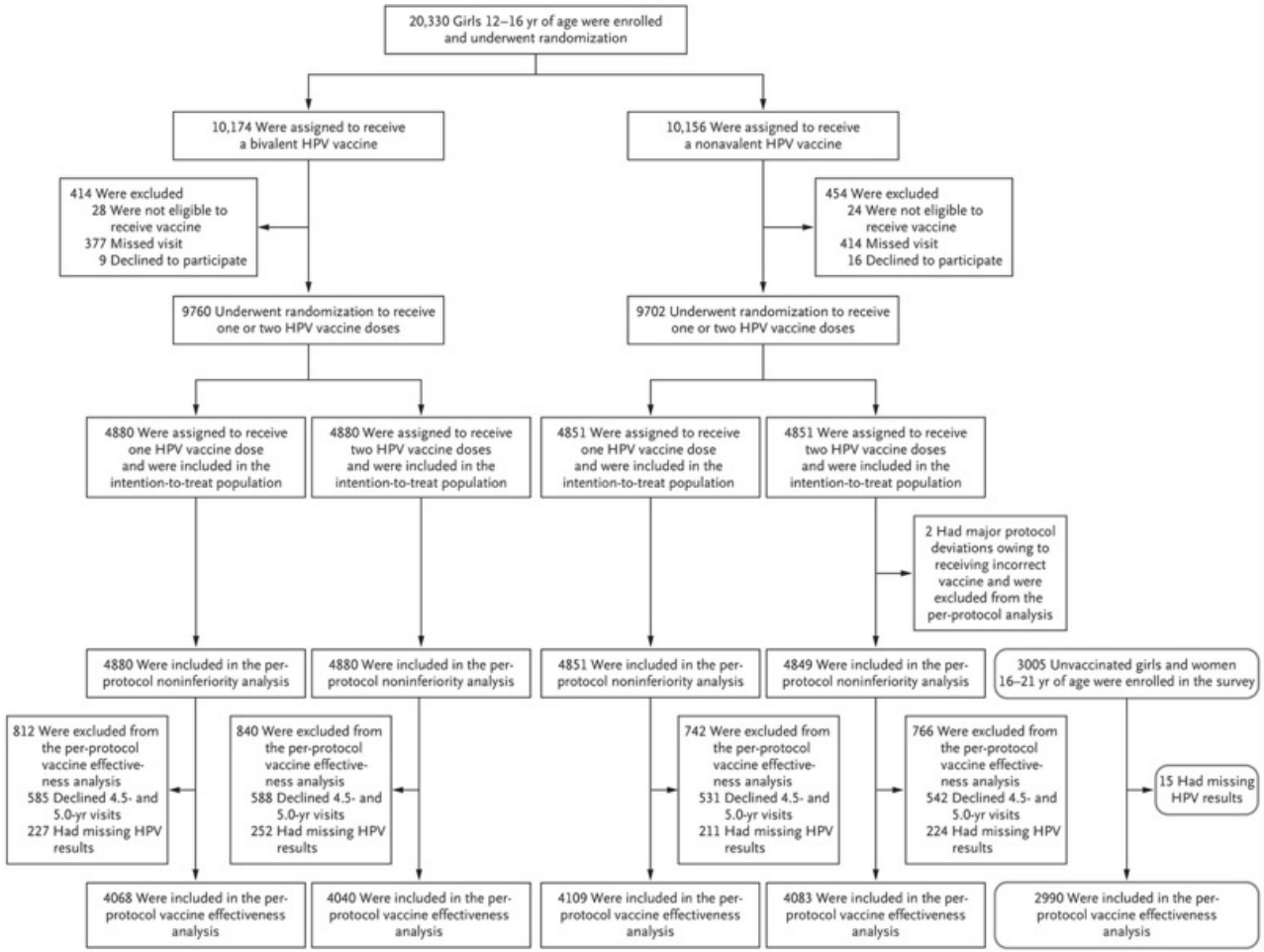
At each visit, a participant-collected cervicovaginal specimen was obtained from trial participants who were 15 years of age or older and from all survey participants, regardless of whether they reported that they had become sexually active. Participants used a Dacron swab for collection, which was immediately placed in 2 ml of PreservCyt. The trial participants and survey participants completed questionnaires that addressed schooling, cigarette smoking, pubertal development, and (among participants ≥15 years of age) sexual history. Adverse events, both serious and nonserious, were coded and reported according to the *International Classification of Diseases, 10th Revision*, and were monitored until resolution, regardless of whether they were considered to be related to vaccination.

HPV Testing

TypeSeq2, a targeted sequencing assay that has been shown to detect 46 HPV types with high positive agreement in repeated testing and against established assays for most carcinogenic and noncarcinogenic genotypes, was used for outcome determination.

End Points and Analyses

The primary end point for the noninferiority analysis was incident, persistent HPV16 or HPV18 infection (HPV16 or HPV18 infection that occurred during the period from month 12 to month 60 and persisted for at least 6 months).



Enrollment, Randomization, and Follow-up.

Trial participants were excluded from the analysis of vaccine effectiveness if they had missing results for human papillomavirus (HPV) infection at both month 54 and month 60 and survey participants were excluded if they had missing results at month 0 (the enrollment visit) and month 6 (the second visit) because they would have contributed no data for the estimation of vaccine effectiveness. The survey participants did not undergo randomization.

Noninferiority Analysis.

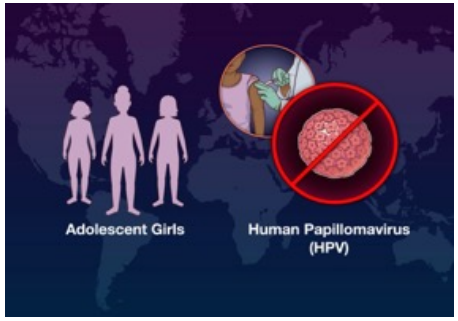
End Point	Bivalent HPV Vaccine				Nonavalent HPV Vaccine			
	No. of Participants	No. of Events	Cumulative Event Rate/100 Participants (95% CI)	Rate Difference (95% CI)†	No. of Participants	No. of Events	Cumulative Event Rate/100 Participants (95% CI)	Rate Difference (95% CI)†
Primary end point: infection with HPV type 16 or 18								
One dose	4880	14	0.29 (0.15 to 0.52)		4851	23	0.48 (0.28 to 0.75)	
Two doses	4880	21	0.42 (0.23 to 0.71)	−0.13 (−0.45 to 0.15)	4849	13	0.27 (0.12 to 0.51)	0.21 (−0.09 to 0.51)
P value‡				<0.001				<0.001
Secondary end point: infection with HPV type 16, 18, 31, 33, 45, 52, or 58								
One dose	4880	824	16.88 (15.71 to 18.11)		4851	79	1.64 (1.25 to 2.10)	
Two doses	4880	721	14.77 (13.63 to 15.96)	2.12 (0.46 to 3.76)	4849	52	1.08 (0.75 to 1.50)	0.56 (0.01 to 1.11)
P value‡				Not calculated				<0.001

Analysis of Vaccine Effectiveness.

End Point	Bivalent HPV Vaccine				Nonavalent HPV Vaccine			
	No. of Participants	No. of Events	Event Rate/100 Participants (95% CI)	Vaccine Effectiveness (95% CI)†	No. of Participants	No. of Events	Event Rate/100 Participants (95% CI)	Vaccine Effectiveness (95% CI)†
Primary end point: infection with HPV type 16 or 18								
Survey	2990	160	5.37 (4.55–6.17)		2990	159	5.32 (4.49–6.17)	
One dose	4068	4	0.10 (0.02–0.21)	98.2 (96.1–99.6)	4109	7	0.16 (0.05–0.30)	97.0 (94.3–99.1)
P value‡				<0.001				<0.001
Survey	2990	162	5.43 (4.56–6.24)		2990	160	5.35 (4.54–6.22)	
Two doses	4040	5	0.12 (0.03–0.23)	97.8 (95.6–99.3)	4083	3	0.08 (0.01–0.16)	98.5 (96.7–99.7)
P value‡				<0.001				<0.001
Secondary end point: infection with HPV type 16, 18, 31, 33, 45, 52, or 58								
Survey	2990	390	13.03 (11.88–14.24)		2990	389	13.01 (11.61–14.29)	
One dose	4068	363	8.93 (8.01–9.79)	31.5 (21.5–40.1)	4109	29	0.72 (0.45–0.99)	94.5 (92.3–96.6)
Survey	2990	385	12.89 (11.59–14.18)		2990	393	13.16 (11.91–14.50)	
Two doses	4040	311	7.69 (6.93–8.56)	40.3 (31.3 to 48.8)	4083	22	0.55 (0.31–0.81)	95.8 (93.8–97.6)

Analysis of Vaccine Effectiveness According to HPV Type.

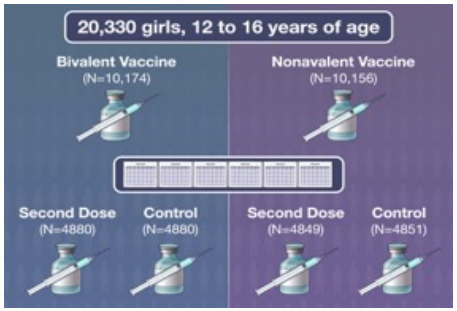
HPV Infection	Bivalent HPV Vaccine				Nonavalent HPV Vaccine			
	No. of Participants	No. of Events	Event Rate/100 Participants (95% CI)	Vaccine Effectiveness (95% CI)	No. of Participants	No. of Events	Event Rate/100 Participants (95% CI)	Vaccine Effectiveness (95% CI)
HPV16								
Survey	2990	109	3.66 (2.91 to 4.33)		2990	109	3.64 (2.97 to 4.33)	
One dose	4068	3	0.08 (0.01 to 0.17)	97.7 (95.1 to 99.7)	4109	4	0.10 (0.02 to 0.20)	97.2 (94.1 to 99.4)
Survey	2990	112	3.73 (3.01 to 4.43)		2990	110	3.67 (2.99 to 4.40)	
Two doses	4040	2	0.06 (0.01 to 0.14)	98.4 (96.1 to 99.8)	4083	1	0.03 (0.00 to 0.08)	99.2 (97.8 to 100)
HPV18								
Survey	2990	61	2.05 (1.56 to 2.64)		2990	61	2.03 (1.54 to 2.56)	
One dose	4068	1	0.02 (0.00 to 0.06)	99.3 (97.0 to 100.0)	4109	2	0.06 (0.00 to 0.14)	97.1 (92.5 to 100)
Survey	2990	61	2.05 (1.52 to 2.57)		2990	61	2.03 (1.51 to 2.59)	
Two doses	4040	2	0.06 (0.00 to 0.15)	97.1 (92.5 to 100.0)	4083	2	0.05 (0.00 to 0.12)	97.6 (93.7 to 100)
HPV31								
Survey	2990	119	3.99 (3.25 to 4.80)		2990	121	4.05 (3.29 to 4.86)	
One dose	4068	100	2.46 (1.92 to 3.03)	38.3 (18.1 to 54.1)	4109	3	0.08 (0.01 to 0.17)	98.0 (95.4 to 99.7)
Survey	2990	119	3.97 (3.19 to 4.77)		2990	123	4.11 (3.36 to 4.83)	
Two doses	4040	28	0.69 (0.46 to 0.99)	82.6 (73.9 to 88.8)	4083	6	0.14 (0.04 to 0.26)	96.6 (93.5 to 99.1)
HPV33								
Survey	2990	30	1.00 (0.67 to 1.39)		2990	29	0.96 (0.62 to 1.33)	
One dose	4068	23	0.57 (0.35 to 0.81)	42.6 (2.1 to 68.4)	4109	1	0.02 (0.00 to 0.07)	97.5 (91.2 to 100)
Survey	2990	29	0.97 (0.63 to 1.32)		2990	29	0.96 (0.60 to 1.31)	
Two doses	4040	30	0.73 (0.44 to 0.99)	24.8 (−26.2 to 58.7)	4083	3	0.07 (0.01 to 0.17)	93.0 (78.6 to 100)
HPV45								
Survey	2990	38	1.28 (0.89 to 1.68)		2990	38	1.28 (0.86 to 1.70)	
One dose	4068	21	0.53 (0.30 to 0.78)	58.8 (28.4 to 78.5)	4109	5	0.12 (0.02 to 0.22)	90.5 (79.4 to 98.2)
Survey	2990	38	1.27 (0.87 to 1.74)		2990	39	1.32 (0.90 to 1.80)	
Two doses	4040	14	0.36 (0.19 to 0.57)	72.1 (46.0 to 87.1)	4083	3	0.08 (0.01 to 0.19)	93.6 (84.7 to 100)
HPV52								
Survey	2990	95	3.16 (2.61 to 3.76)		2990	94	3.13 (2.48 to 3.76)	
One dose	4068	128	3.16 (2.65 to 3.75)	0.3 (−31.5 to 23.7)	4109	3	0.08 (0.00 to 0.17)	97.3 (93.9 to 100)
Survey	2990	94	3.14 (2.50 to 3.84)		2990	95	3.18 (2.48 to 3.84)	
Two doses	4040	143	3.55 (2.99 to 4.14)	−13.2 (−49.6 to 13.5)	4083	2	0.05 (0.00 to 0.12)	98.5 (96.1 to 100)
HPV58								
Survey	2990	88	2.95 (2.35 to 3.60)		2990	89	2.98 (2.35 to 3.57)	
One dose	4068	143	3.51 (2.92 to 4.09)	−19.3 (−53.8 to 7.5)	4109	12	0.29 (0.13 to 0.47)	90.2 (83.4 to 95.6)
Survey	2990	84	2.81 (2.22 to 3.48)		2990	89	2.99 (2.44 to 3.62)	
Two doses	4040	127	3.15 (2.60 to 3.76)	−12.0 (−48.2 to 16.6)	4083	5	0.13 (0.05 to 0.26)	95.5 (90.7 to 98.6)
HPV6								
Survey	2990	61	2.03 (1.53 to 2.62)		2990	61	2.05 (1.49 to 2.55)	
One dose	4068	63	1.55 (1.21 to 1.96)	23.6 (−7.9 to 45.4)	4109	8	0.20 (0.08 to 0.37)	90.0 (81.5 to 96.3)
Survey	2990	61	2.05 (1.54 to 2.59)		2990	62	2.09 (1.61 to 2.62)	
Two doses	4040	74	1.82 (1.40 to 2.23)	11.4 (−27.0 to 36.5)	4083	1	0.03 (0.00 to 0.10)	98.7 (95.0 to 100)
HPV11								
Survey	2990	12	0.42 (0.21 to 0.66)		2990	12	0.41 (0.19 to 0.64)	
One dose	4068	5	0.13 (0.03 to 0.26)	69.2 (23.0 to 94.5)	4109	0	0.00†	100†
Survey	2990	12	0.39 (0.15 to 0.63)		2990	12	0.41 (0.19 to 0.62)	
Two doses	4040	11	0.28 (0.13 to 0.47)	27.1 (−86.7 to 68.7)	4083	4	0.10 (0.01 to 0.22)	76.3 (27.5 to 97.1)

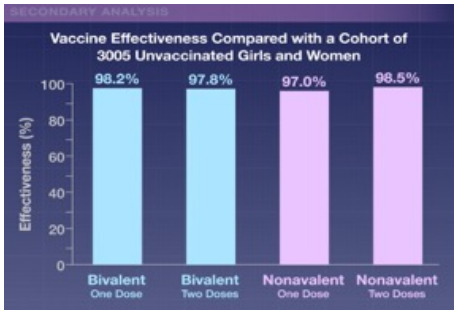

Adolescent Girls
Human Papillomavirus (HPV)


ESCUDDO TRIAL
• Randomized
• Controlled
• Double-blind
• Noninferiority

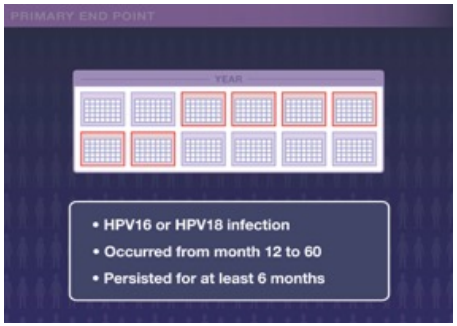

PRIMARY END POINT
≈
Both single doses were noninferior to the two-dose regimens.

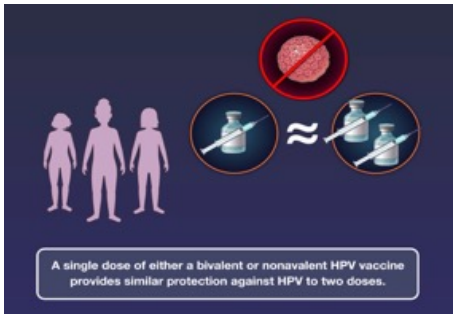

Only 27% of eligible girls worldwide have received an HPV vaccine.
A single dose may provide protection.


20,330 girls, 12 to 16 years of age
Bivalent Vaccine (N=10,174)
Nonavalent Vaccine (N=10,156)
Second Dose (N=4880)
Control (N=4880)
Second Dose (N=4849)
Control (N=4851)

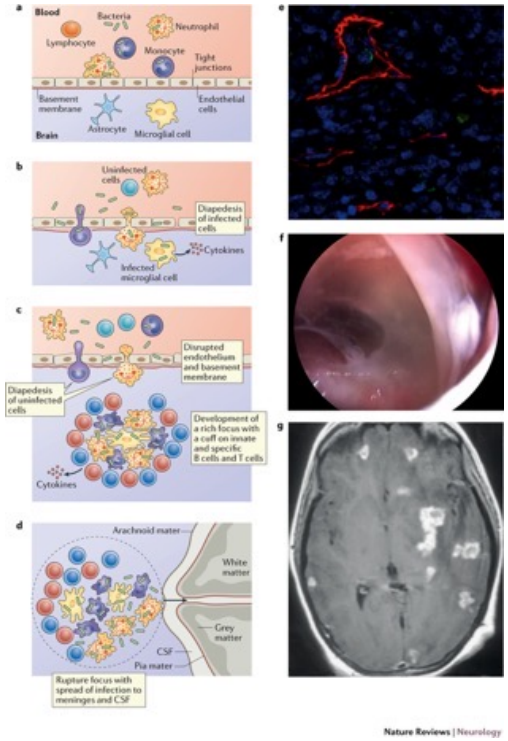

SECONDARY ANALYSIS
Vaccine Effectiveness Compared with a Cohort of 3005 Unvaccinated Girls and Women
Effectiveness (%)
100
80
60
40
20
0
98.2%
97.8%
97.0%
98.5%
Bivalent One Dose
Bivalent Two Doses
Nonavalent One Dose
Nonavalent Two Doses

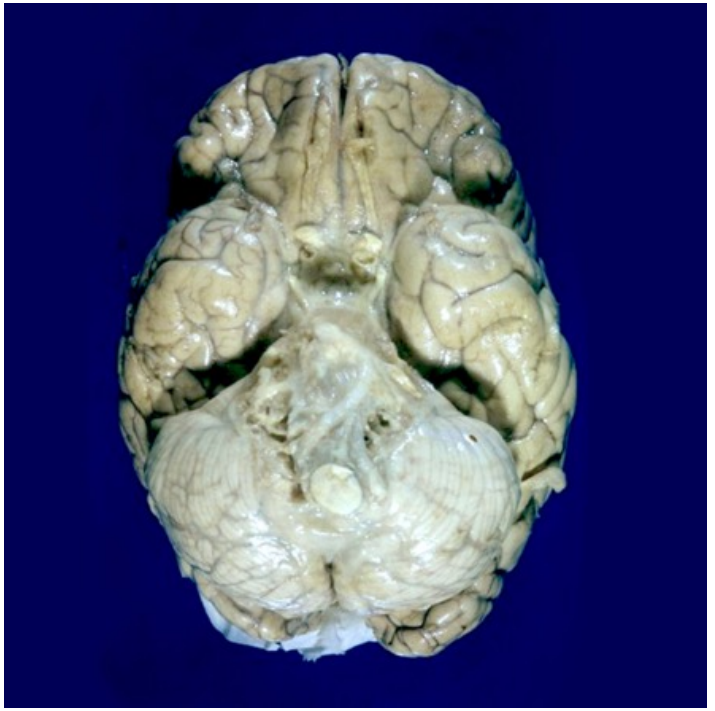

ESCUDDO TRIAL
vs.


PRIMARY END POINT
YEAR
• HPV16 or HPV18 infection
• Occurred from month 12 to 60
• Persisted for at least 6 months


≈
A single dose of either a bivalent or nonavalent HPV vaccine provides similar protection against HPV to two doses.

Tuberculous Meningitis (TBM) is a severe infection and inflammation of the brain/spinal cord linings (meninges) caused by *Mycobacterium tuberculosis*, often spreading from the lungs; it develops slowly, causing headaches, fever, stiff neck, confusion, and light sensitivity, and requires prompt, long-term treatment with anti-TB drugs, as it's a leading cause of death or disability from TB without treatment, especially in immunocompromised individuals.

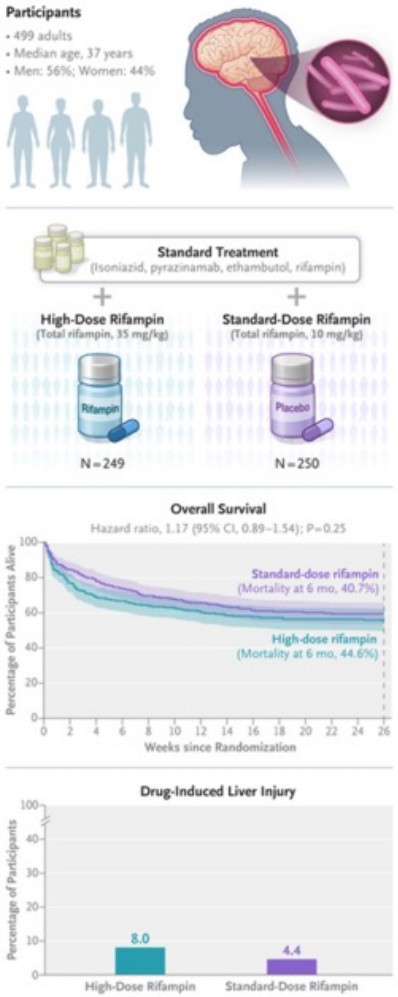




Trial of High-Dose Oral Rifampin in Adults with Tuberculous Meningitis

Tuberculous meningitis is often lethal, and many survivors have disabilities despite antimicrobial treatment and adjunctive glucocorticoid therapy. Standard-dose rifampin has limited central nervous system penetration. Whether high-dose rifampin could improve survival outcomes is unknown.

We performed a double-blind, randomized, placebo-controlled clinical trial involving adults with tuberculous meningitis in Indonesia, South Africa, and Uganda. We assigned persons with and those without human immunodeficiency virus (HIV) coinfection to receive standard daily isoniazid, rifampin (at a dose of 10 mg per kilogram of body weight), ethambutol, and pyrazinamide plus either additional rifampin (for a cumulative dose of 35 mg per kilogram; high-dose group) or matched placebo (standard-dose group) for 8 weeks; participants in both groups received standard therapy for the remainder of the 9- to-12-month treatment course. The primary outcome was 6-month mortality.



Tuberculous meningitis is a severe manifestation of tuberculosis. Despite guidelines recommending treatment with isoniazid, pyrazinamide, ethambutol, and rifampin (at a dose of 10 mg per kilogram of body weight daily), outcomes of tuberculous meningitis remain poor, with mortality as high as 50% among persons with human immunodeficiency virus (HIV). Rifampin (also known as rifampicin) is a cornerstone drug for the treatment of tuberculous meningitis, as evidenced by the higher mortality in rifampin-resistant disease, but it has limited penetration into cerebrospinal fluid (CSF), with approximately 5% of the levels found in plasma. Consequently, standard rifampin dosing leads to undetectable levels in CSF in the majority of persons with tuberculous meningitis, a finding that arouses concerns regarding the adequacy of standard rifampin dosing.

Emerging evidence suggests that higher rifampin doses may improve treatment outcomes among patients with tuberculous meningitis. Four phase 2 trials have shown a dose–exposure relationship for rifampin, with higher doses leading to higher drug levels in plasma and CSF. A trial in Vietnam involving 817 persons with tuberculous meningitis who received oral rifampin at a dose of 15 mg per kilogram showed no benefit. However, a meta-analysis of phase 2 trials in Indonesia indicated that a rifampin dose of 30 mg per kilogram daily resulted in a total (protein-unbound plus bound) rifampin plasma exposure that was higher by a factor of 4.7 and was associated with a 40% higher 6-month survival — although the uncertainty in the estimate of the effect was large (relative standard error, 86%). Given the mixed evidence, a well-powered, randomized clinical trial evaluating high-dose rifampin was deemed necessary.

Trial Population and Setting

The trial aimed to enroll 500 eligible participants 18 years of age or older with tuberculous meningitis at nine hospitals. Eligibility criteria included microbiologically confirmed tuberculosis (defined by a positive result in a CSF sample with the use of the Xpert MTB/RIF Ultra assay [Cepheid], a Mycobacteria Growth Indicator Tube culture [Becton Dickinson], or smear microscopy) or tuberculous meningitis considered to be probable or possible on the basis of abnormal CSF values and clinical findings, with antituberculous treatment planned.

Intervention and Randomization

We randomly assigned participants in a 1:1 ratio to receive oral rifampin either at a high dose or at a standard dose for the first 8 weeks; participants in both groups received standard therapy for the remainder of the treatment course, which was 9 to 12 months in total. Participants in the high-dose group received oral rifampin at a dose of approximately 35 mg per kilogram daily for the first 8 weeks.

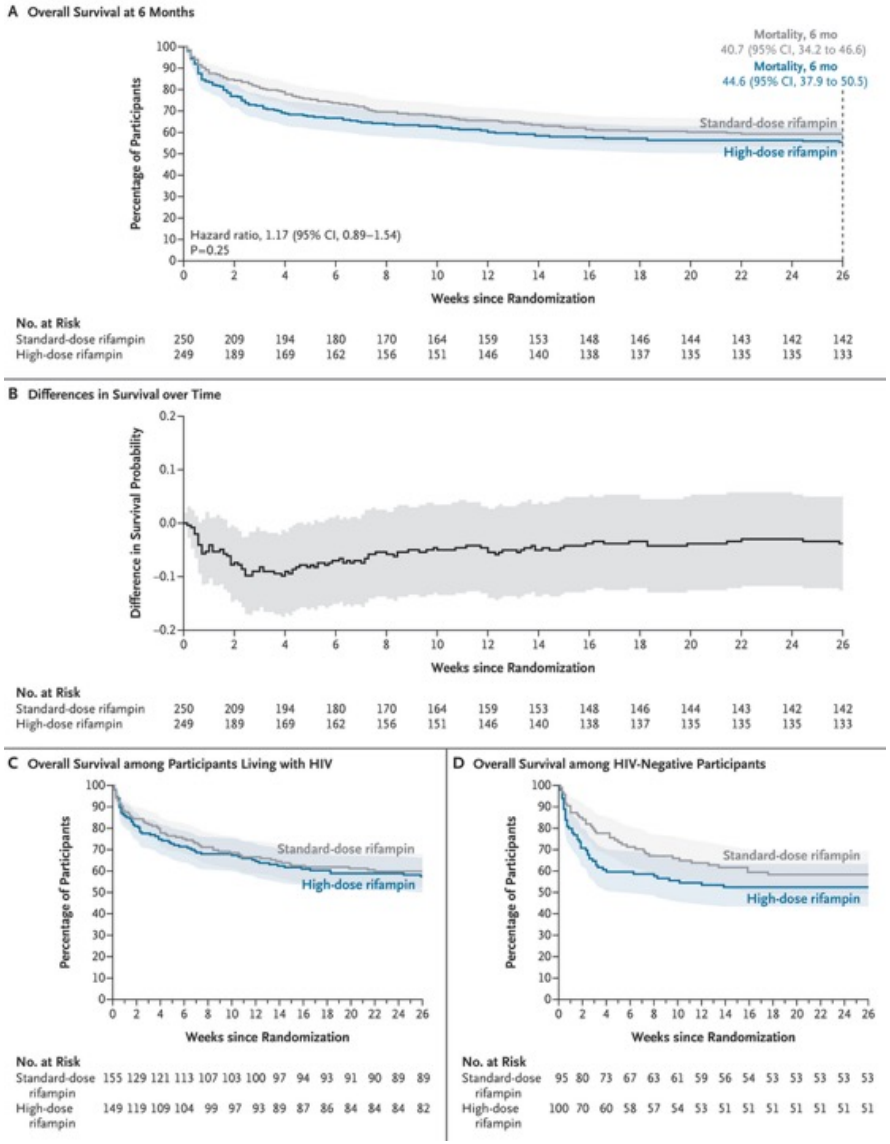
Outcomes

The primary outcome was 6-month mortality. Secondary outcomes included 12-month mortality, functional status as measured by the modified Rankin scale (range, 0 to 6, with higher scores indicating worse disability) at week 24 and the Liverpool Outcome score (range, 1 [death] to 5 [full recovery] in 15 questions) at 2 weeks and at 6 months, neurocognitive performance at 2 months and at 12 months, duration of hospitalization, treatment discontinuation for any cause for 5 days or more in the first 8 weeks, rehospitalization due to neurologic decline, and the incidence of adverse events of grade 3 or higher and serious adverse events, including hepatotoxic effects.

Characteristic	High-Dose Rifampin (N=249)	Standard-Dose Rifampin (N=250)
Median age (IQR) — yr	38 (28–46)	35 (28–45)
Female sex — no. (%)	101 (40.6)	121 (48.4)
Median weight (IQR) — kg	54 (49–60)	55 (45–62)
MRC disease severity grade — no. (%)†		
Grade 1	50 (20.1)	53 (21.2)
Grade 2	148 (59.4)	158 (63.2)
Grade 3	51 (20.5)	39 (15.6)
Glasgow Coma Scale score <15 — no./total no. (%)	164/244 (67.2)	160/247 (64.8)
Living with HIV — no. (%)	149 (59.8)	155 (62.0)
Receiving antiretroviral therapy — no./total no. (%)	64/149 (43.0)	61/155 (39.4)
Median CD4 cell count (IQR) — cells/mm³‡	101 (38–176)	85 (43–204)
Tuberculosis treatment at enrollment — no. (%)	175 (70.3)	173 (69.2)
Median doses in previous 7 days (IQR)	3 (1–4)	3 (1–4)
Diagnostic tuberculous meningitis category		
Definite	114 (45.8)	104 (41.6)
Probable	89 (35.7)	91 (36.4)
Possible	44 (17.7)	54 (21.6)
Not tuberculous meningitis§	2 (0.8)	1 (0.4)
Median creatinine (IQR) — mg/dl¶	0.70 (0.55–0.89)	0.68 (0.55–0.80)
Median sodium (IQR) — mmol/liter‖	133 (128–137)	133 (128–138)
Median total bilirubin (IQR) — mg/dl**	0.5 (0.3–1.0)	0.5 (0.3–0.8)
Median alanine aminotransferase (IQR) — U/liter††	25 (16–43)	24 (15–40)
CSF test results		
Median white-cell count (IQR) — cells/mm³‡‡	50 (4–177)	59 (11–203)
<5 White cells/mm³ — no./total no. (%)	63/245 (25.7)	50/248 (20.2)
Median protein (IQR) — mg/dl§§	135 (85–239)	140 (82–243)
Median glucose (IQR) — mg/dl¶¶	41.0 (24.8–61.0)	41.4 (25.0–58.0)
Median ratio of CSF to plasma glucose (IQR)‖‖	0.4 (0.2–0.5)	0.4 (0.2–0.5)

Clinical Adverse Events and Laboratory Abnormalities.

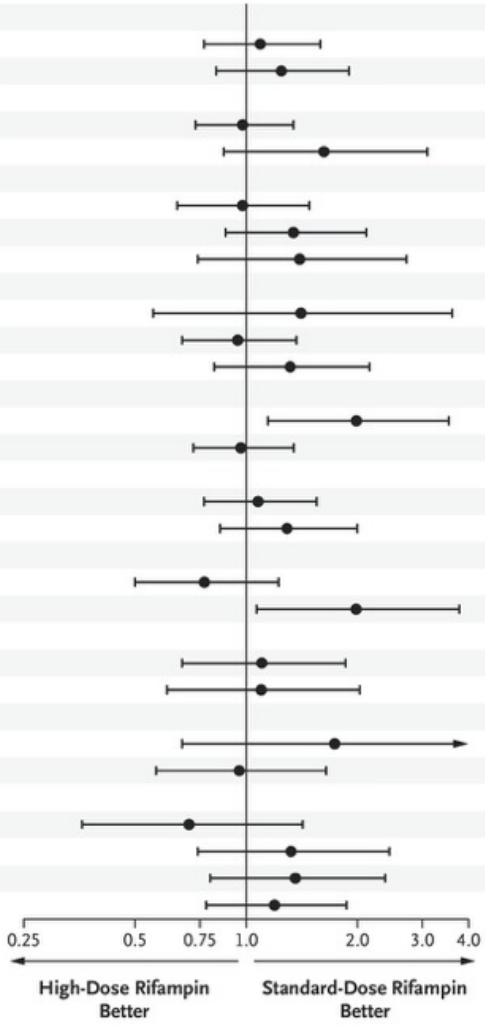
Adverse Event	High-Dose Rifampin (N=249)	Standard-Dose Rifampin (N=250)	P Value
Serious adverse events			
Participants with any serious adverse event — no. (%)	84 (33.7)	101 (40.4)	0.12
No. of serious adverse events	102	115	
Serious adverse events probably or definitely related to treatment — no./total no. (%)	7/102 (6.9)	5/115 (4.3)	
Most frequently reported grade 3–5 adverse events			
No. of grade 3–5 adverse events	192	194	
Participants with ≥1 adverse event — no. (%)	123 (49.4)	129 (51.6)	
Neurologic events — no. (%)			
Cerebrovascular accident	9 (3.6)	10 (4.0)	0.82
General seizures	5 (2.0)	6 (2.4)	0.77
Partial seizures	3 (1.2)	2 (0.8)	0.65
Space-occupying lesion	3 (1.2)	2 (0.8)	0.65
Immune reconstitution inflammatory syndrome	5 (2.0)	4 (1.6)	0.73
Aspiration pneumonia — no. (%)	16 (6.4)	4 (1.6)	0.006
Sepsis — no. (%)			
Systemic inflammatory response syndrome without identified bacteremia	6 (2.4)	7 (2.8)	0.78
Sepsis with bacteremia	4 (1.6)	10 (4.0)	0.11
Shock with multiorgan failure	14 (5.6)	13 (5.2)	0.83
Hepatic events of grade 3 or 4 — no. (%)			
Alanine aminotransferase ≥5×ULN	13 (5.2)	15 (6.0)	0.71
Alkaline phosphatase ≥5×ULN	0	0	—
Total bilirubin ≥2.6×ULN	24 (9.6)	9 (3.6)	0.007
Drug-induced liver injury †	20 (8.0)	11 (4.4)	0.09
Deaths related to drug-induced liver injury	0	0	—
Trial regimen discontinuation for >5 days	6 (2.4)	4 (1.6)	0.52



Kaplan–Meier Curves for 6-Month Survival According to Treatment Group and HIV Status.

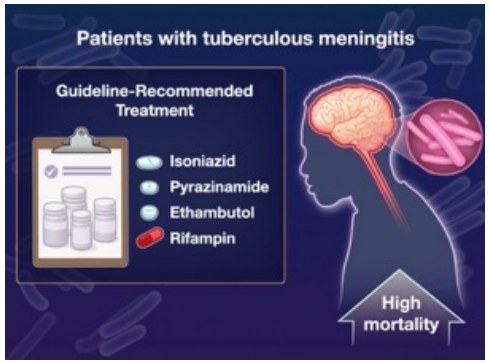
Panel A shows overall 6-month survival estimated with Kaplan–Meier curves. Panel B shows the difference between the high-dose group and the standard-dose group in survival over time. In the first 21 days, 68 deaths (Kaplan–Meier estimate, 27.6%; 95% CI, 21.8 to 33.0) occurred in the high-dose group and 48 deaths (Kaplan–Meier estimate, 19.4%; 95% CI, 14.3 to 24.2) occurred in the standard-dose group. Data from 8 participants in each group were censored before 6 months (range, 1 day to 162 days). Panels C and D show overall survival according to HIV status. In all panels, shading indicates 95% confidence intervals.

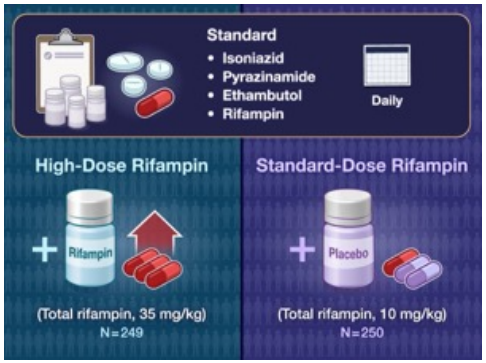
Subgroup	High-Dose Rifampin	Standard-Dose Rifampin	Hazard Ratio for Death (95% CI)
	no. of deaths/no. of participants (%)		
Sex			
Male	64/148 (43.2)	54/129 (41.9)	1.11 (0.77–1.59)
Female	45/101 (44.6)	46/121 (38.0)	1.26 (0.83–1.90)
Glasgow Coma Scale score			
<15	82/164 (50.0)	81/160 (50.6)	0.99 (0.73–1.34)
15	22/80 (28)	17/87 (20)	1.64 (0.87–3.10)
Tuberculous meningitis category			
Definite	47/114 (41.2)	45/104 (43.3)	0.99 (0.65–1.48)
Probable	44/89 (49)	36/91 (40)	1.36 (0.88–2.11)
Possible	18/44 (41)	18/54 (33)	1.41 (0.74–2.72)
MRC severity grade			
Grade 1	10/50 (20)	8/53 (15)	1.43 (0.56–3.61)
Grade 2	56/148 (37.8)	65/158 (41.1)	0.96 (0.67–1.37)
Grade 3	43/51 (84)	27/39 (69)	1.33 (0.82–2.16)
Cerebrospinal fluid white cells			
<5 cells/μl	37/63 (59)	18/50 (36)	2.01 (1.14–3.54)
≥5 cells/μl	72/182 (39.6)	82/198 (41.4)	0.98 (0.72–1.35)
HIV status			
Positive	62/149 (41.6)	61/155 (39.4)	1.09 (0.77–1.55)
Negative	47/100 (47.0)	39/95 (41)	1.31 (0.85–2.00)
ART status			
Not receiving ART	34/83 (41)	45/92 (49)	0.78 (0.50–1.22)
Receiving ART	27/64 (42)	15/61 (25)	2.01 (1.07–3.78)
CD4 count			
<100 cells/mm^3	29/55 (53)	30/61 (49)	1.12 (0.67–1.86)
≥100 cells/mm^3	24/73 (33)	19/64 (30)	1.11 (0.61–2.03)
HIV-1 viral load			
Undetectable	13/38 (34)	6/27 (22)	1.76 (0.67–4.62)
Detectable	25/62 (40)	30/72 (42)	0.97 (0.57–1.65)
Site of trial			
Jakarta, Indonesia	14/35 (40)	19/35 (54)	0.71 (0.36–1.42)
Durban, South Africa	23/56 (41)	20/56 (36)	1.34 (0.74–2.44)
Bandung, Indonesia	28/58 (48)	24/59 (41)	1.38 (0.80–2.38)
Kampala, Uganda	44/100 (44.0)	37/100 (37.0)	1.21 (0.78–1.87)

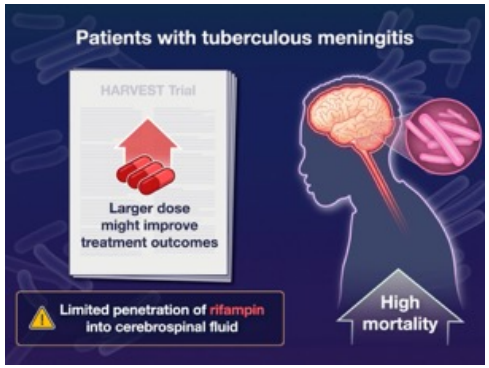


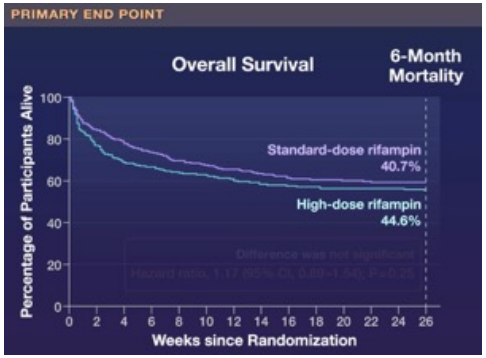
Treatment Effect According to Baseline Characteristics of the Participants.

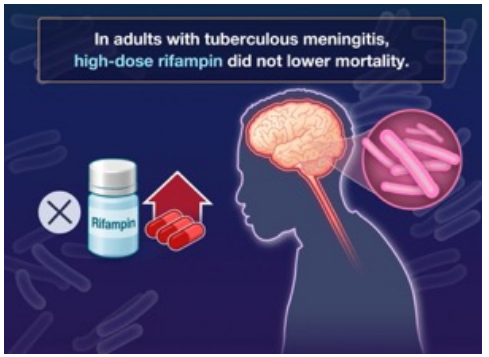
Interactions between the treatment group and the prespecified subgroups defined by the characteristics of the participants at baseline were assessed to determine whether the treatment effect (hazard ratio for death with high-dose rifampin vs. standard-dose rifampin) was dependent on those characteristics. Results in the subgroups were generally consistent with those for the overall outcome, with none showing a benefit with high-dose rifampin. Figure S1 in the Supplementary Appendix shows Kaplan–Meier curves according to the subgroups. Baseline viral suppression (detectable vs. undetectable HIV viral load) was selected as a post hoc subgroup, on the basis of observed difference in the antiretroviral therapy subgroup. Medical Research Council (MRC) disease severity grade 1 indicates that the patient is alert and oriented without focal neurologic deficit, grade 2 that the patient has a Glasgow Coma Scale score of 11 to 14 with or without focal neurologic deficit or a score of 15 with focal neurologic deficit, and grade 3 that the patient has a score of less than 10 with or without focal neurologic deficit. Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating poorer neurologic function. ART denotes antiretroviral therapy.

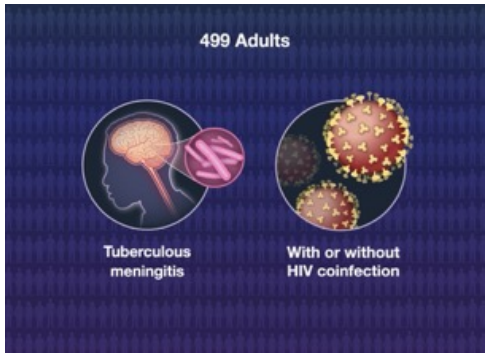

Patients with tuberculous meningitis
Guideline-Recommended Treatment
Isoniazid
Pyrazinamide
Ethambutol
Rifampin
High mortality

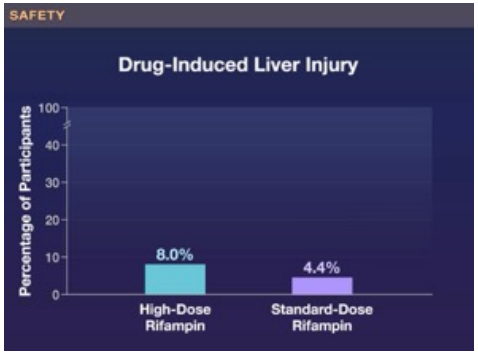

Standard
Isoniazid
Pyrazinamide
Ethambutol
Rifampin
Daily
High-Dose Rifampin
Rifampin
(Total rifampin, 35 mg/kg)
N=249
Standard-Dose Rifampin
Placebo
(Total rifampin, 10 mg/kg)
N=250


Patients with tuberculous meningitis
HARVEST Trial
Larger dose might improve treatment outcomes
Limited penetration of rifampin into cerebrospinal fluid
High mortality


PRIMARY END POINT
Overall Survival
6-Month Mortality
Percentage of Participants Alive
Standard-dose rifampin
40.7%
High-dose rifampin
44.6%
Weeks since Randomization

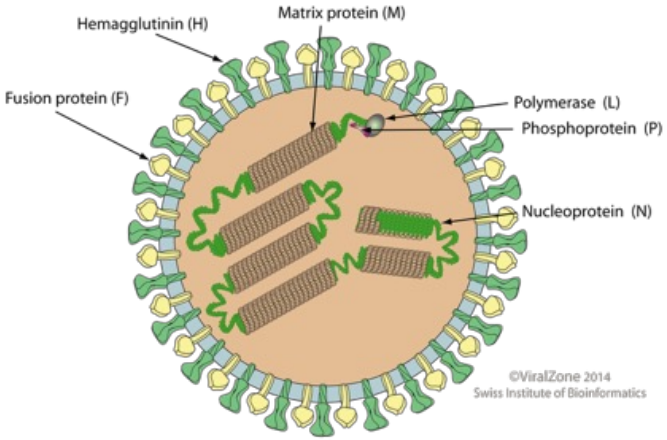

In adults with tuberculous meningitis, high-dose rifampin did not lower mortality.
Rifampin

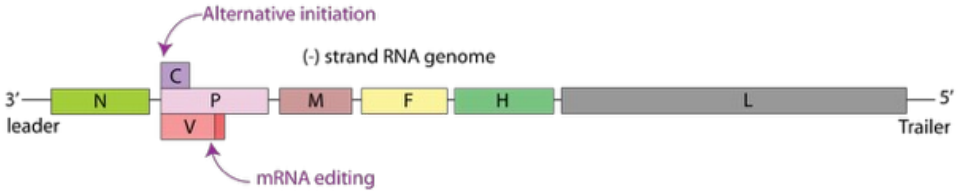

499 Adults
Tuberculous meningitis
With or without HIV coinfection


SAFETY
Drug-Induced Liver Injury
Percentage of Participants
8.0%
4.4%
High-Dose Rifampin
Standard-Dose Rifampin

Das Masernvirus ist ein ausschließlich humanpathogener, etwa 100–250 Nanometer großer Erreger der Masern aus der Familie der Paramyxoviridae. Das einzige Reservoir bildet der infizierte Mensch. Experimentell können auch Hunde infiziert werden, bilden jedoch keine Symptome aus. Morbillivirus ist eine Virus-Gattung der Familie Paramyxoviridae, Ordnung Mononegavirales. Es handelt sich um hochansteckende behüllte Viren mit einem helikalen Kapsid. Das Genom besteht aus einer einzelsträngigen, nicht-segmentierten RNA mit negativer Polarität.

Morbillivirus ist eine Virus-Gattung der Familie Paramyxoviridae, Ordnung Mononegavirales. Es handelt sich um hochansteckende behüllte Viren mit einem helikalen Kapsid. Das Genom besteht aus einer einzelsträngigen, nicht-segmentierten RNA mit negativer Polarität (ss(−)RNA). Die Virushülle besitzt sogenannte Spikes, deren Glycoproteine Hämagglutinin-, Neuraminidase- und hämolytische Aktivität besitzen.



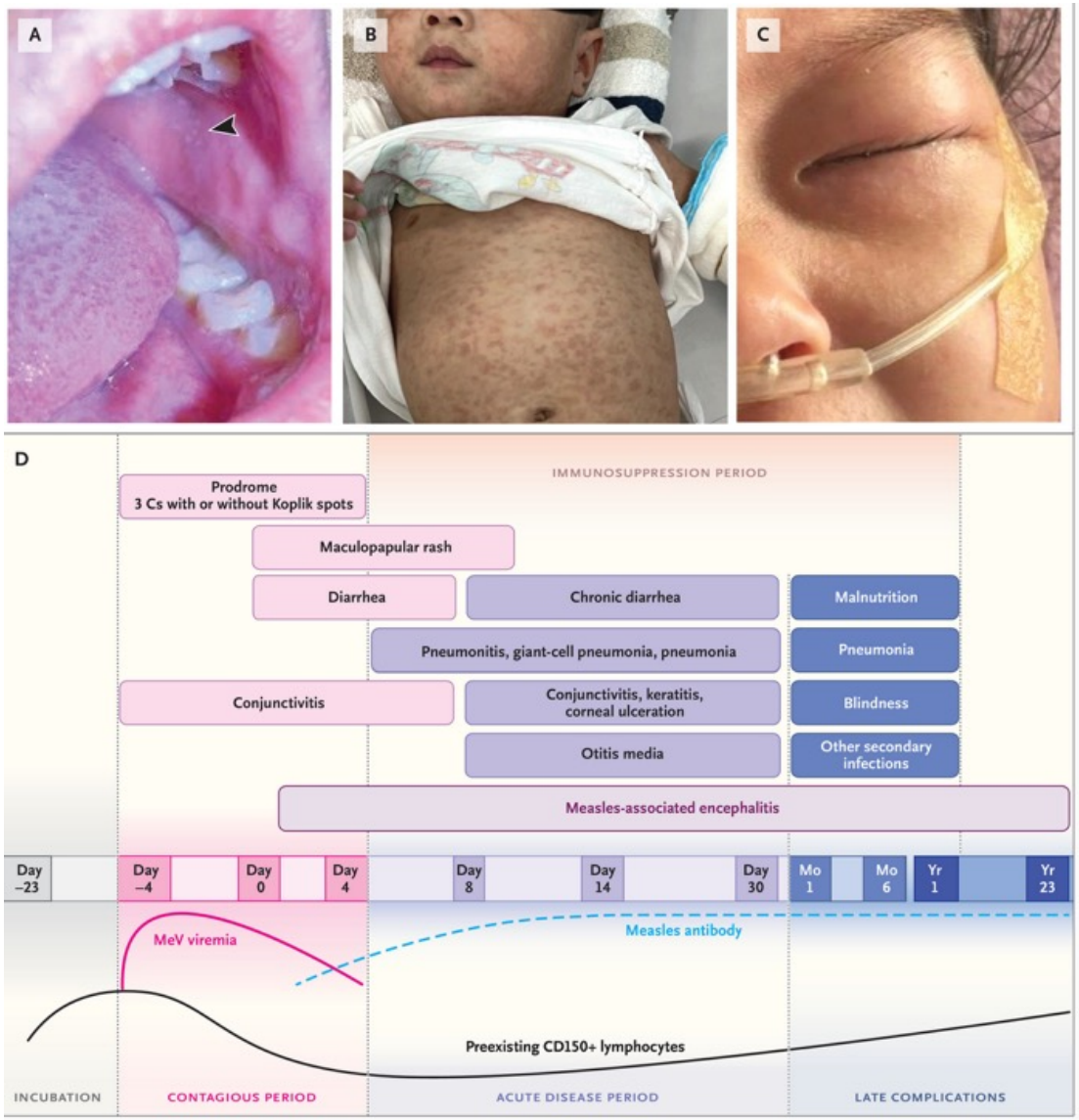


The measles vaccine (MMR) works by targeting conserved, essential epitopes on the virus's surface proteins, primarily the Hemagglutinin (H) protein, which mediates cell attachment, and also the Fusion (F) protein, triggering neutralizing antibodies against these key areas, including conserved regions near the receptor-binding site (RBS) and other stable sites, ensuring broad protection across different measles virus genotypes.

REVIEW ARTICLE

Measles 2025

Measles is a highly contagious virus with a primary case reproduction number (i.e., the average number of secondary cases per case patient) of 12 to 18. It is currently spreading rapidly owing to reduced measles vaccination coverage, which is due primarily to the disruption of local immunization programs by the coronavirus disease 2019 (Covid-19) pandemic and of growing vaccine hesitancy. Since 2024, all World Health Organization (WHO) regions have reported increased numbers of measles cases, with 395,521 laboratory-confirmed measles cases reported in 2024 and 16,147 reported during the first 2 months of 2025. Patients in more than half the reported cases were hospitalized, so the true number is probably much higher.
This review covers clinical presentations and complications of measles, current recommendations, and the epidemiologic background of measles. It also addresses the current debates on immunization and the treatment of measles and presents information on the origins of the various measles vaccines and updates on measles diagnostic testing and molecular genotypes.



Clinical Features and Pathogenesis of Measles.

Features of measles include Koplik spots on the buccal mucosa (Panel A); rash on the trunk, spreading to the face, head, arms, and legs (Panel B); and conjunctivitis (Panel C). Day 0 denotes the day the measles rash appears; Day −4 is the probable start of infectiousness, Day 4 is the probable end of infectiousness, and Day −23 is the earliest possible exposure day (Panel D). CD150+ lymphocytes are T and B memory lymphocytes targeted by the measles virus. 3 Cs denotes cough, coryza, and conjunctivitis, and MeV measles virus. Images in Panels A, B, and C were provided by Du Tuan Quy, M.D., with the approval of Le Nguyen Thanh Nhan, M.D., Ph.D., Children's Hospital 1, Ho Chi Minh City, Vietnam.

KEY POINTS

Measles 2025

- Measles causes a range of serious health issues, including immune amnesia that may last up to 1 year in fully recovered patients and increased susceptibility to sometimes severe secondary infections. Research on restoring immunity more rapidly is needed.
- Measles vaccine has a long safety history and is highly effective against all circulating measles genotypes.
- Measles is highly contagious; therefore, a high coverage level (>95%) of both recommended doses of measles vaccine is necessary to prevent community transmission.
- Vitamin A supplementation is recommended for all persons who have measles to reduce complications and the risk of death, particularly in persons who have deficient levels of vitamin A, such as persons living in low- and middle-income countries. Vitamin A does not prevent measles infection. More data are needed regarding the benefits of vitamin A in persons living in developed countries who have measles.
- Waning levels of maternal measles antibodies at 3 to 4 months of age has increased measles risk in young infants. Further research on the effectiveness of early measles vaccination is needed.
- Additional randomized, controlled trials are needed to evaluate the clinical efficacy of vaccine microneedle patches, which may help to increase vaccination coverage.

R value = 12

Low vitamin A is risk

2 doses recommended

Impf plaster kommt

Incidence of Severe Complications Associated with Measles

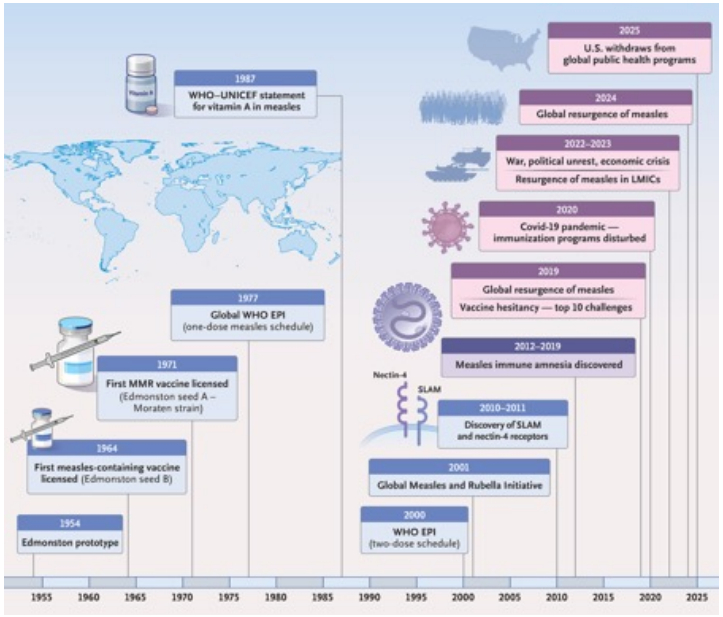
Complications	Incidence in Developed Countries	Comments
Pneumonia	1–6 per 100 measles cases[5]	Among the most common complications during the first month of measles; most common cause of measles hospitalization
Diarrhea	8–10 per 100 measles cases[5]	Common complication during the first month of measles
Keratitis or keratoconjunctivitis	3–10 per 100 measles cases [6-9]	Keratoconjunctivitis may appear in the prodromal stages of measles and persist for as long as 3 months[6]; keratitis with retinitis and optic neuritis also has been reported.[7-9]
Corneal ulceration	Rare	Documented in 1–4 per 100 measles cases in the 1980s in Africa and South Asia[10,11]; measles can cause corneal ulceration directly and facilitate a secondary infection (such as herpes simplex keratitis) that leads to corneal ulceration[10,11]
Blindness	Rare	Measles is a leading cause of childhood blindness in places where measles is endemic; results of surveys conducted in schools in Africa in the 1970s suggested that measles was the cause of 33 to 79% cases of blindness.[11]
Otitis media	7–9 per 100 measles cases[5]	One of the most common complications during the first month of measles; can lead to sensorineural deafness, which was observed in 5 to 10% of measles cases in the United States before the introduction of measles vaccination programs[5]
Death	1–3 per 1000 measles cases[5]	16 per 1000 measles cases in low-income countries[12]; 9 per 1000 measles cases in middle-income countries[12]; up to 180 per 1000 measles cases reported in the context of humanitarian relief efforts during major outbreaks[13]
Malnutrition	8–10 per 100 measles cases	
Acute postinfectious measles encephalitis	1 per 1000 measles cases[14]	Develops within the first week of measles, after the appearance of the first symptoms, and is associated with 20% mortality[14]
Measles-inclusion body encephalitis	1 per 1000 measles cases[14]	Develops within 7 days to 6 months after onset of measles and is associated with 100% mortality[14]
Subacute sclerosing panencephalitis	7–11 per 100,000 measles cases[5,14]	Develops within 7–10 years after measles and is associated with 100% mortality within 1–3 years after onset[14]; young children with measles (<2 years of age) are at increased risk

Summary of Current Measles Vaccination Recommendations in the United States.

Recommendation	Schedule and Dose
Preschool children	
Routine childhood schedule	Two-dose schedule — First dose at 12 to 15 months of age (MMR vaccine), second dose at 4 to 6 years of age (MMR-V vaccine)
In outbreak locations or before international travel	Additional dose is given as early as 6 months of age to all children younger than 12 months of age; routine two-dose schedule is still recommended, but earlier second dose is recommended†
Healthy adults	Two-dose schedule unless evidence of immunity; no booster program for those with evidence of previous vaccination on two-dose schedule‡
Special populations	
Health care workers born before 1957	One or two doses of measles vaccine unless evidence of immunity‡
Health care workers born in 1957 or later	Two-dose schedule unless evidence of immunity†‡
Received measles vaccine between 1967 and 1989	One or two doses of measles vaccine unless evidence of immunity‡
≥12 mo of age with HIV infection	Two-dose schedule: first dose at 12 months of age (MMR vaccine), second dose can be earlier than routine (at 13 months of age; MMR vaccine)†§
International travelers	Two-dose schedule unless evidence of immunity†‡
Family carers of immunocompromised patients	Two-dose schedule unless evidence of immunity†‡

U.S. Recommendations for Vitamin A Supplementation in Patients with Measles.

Age Group	Dose	Frequency
Children		
<6 mo	50,000 IU (15,000 μg RAE)	Daily for 2 days
6–11 mo	100,000 IU (30,000 μg RAE)	Daily for 2 days
>12 mo	200,000 IU (60,000 μg RAE)	Daily for 2 days
Previous vitamin A deficiency or eye complications caused by measles	Third dose	2–4 wk after the second dose
Adults†	No recommendation	No recommendation



Key Events in Measles Research.

Covid-19 denotes coronavirus disease 2019, EPI Expanded Programme on Immunization, LMICs low- and middle-income countries, MMR measles–mumps–rubella, SLAM signaling lymphocytic activation molecule, UNICEF United Nations Children's Fund, and WHO World Health Organization.

Conclusions and Perspectives

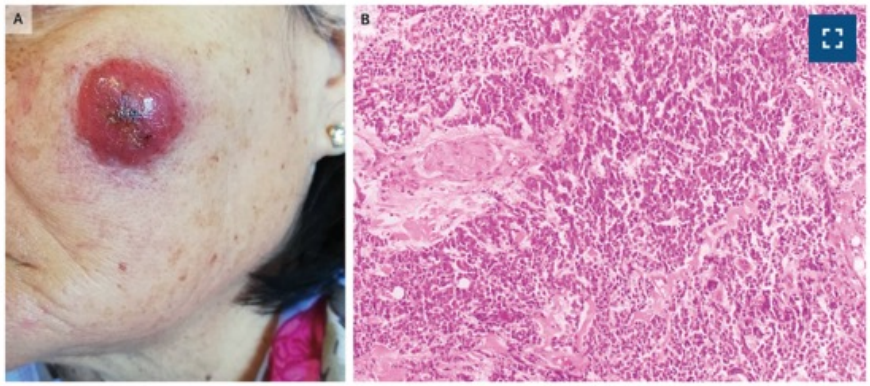
There has been little improvement in global measles control over the past two decades. With a declining environment for global health, it is possible that the situation will get worse. Estimates of measles morbidity and mortality associated with vaccine hesitancy are needed to help contain vaccine hesitancy. Enhanced research during measles outbreaks is crucial to address population immunity gaps and improve vaccine coverage in the current measles vaccination program. Rapid diagnostic tests could be used routinely as part of measles global surveillance and could improve the timing of measles outbreak responses.

Postmeasles pneumonia has been shown to be largely due to *Streptococcus pneumoniae*. The use of a booster dose of pneumococcal conjugate vaccine for patients recovering from measles to help overcome temporary immunologic amnesia and possibly prevent fatal postmeasles pneumonia is a potential strategy. Clinical trials are needed to determine the appropriate time to administer pneumococcal conjugate vaccine during measles recovery.

Measles disease is most severe in young infants. Studies from West Africa have shown that measles vaccine can be highly effective, even when it is given as early as 4 months of age. This finding needs to be reevaluated in the modern era.

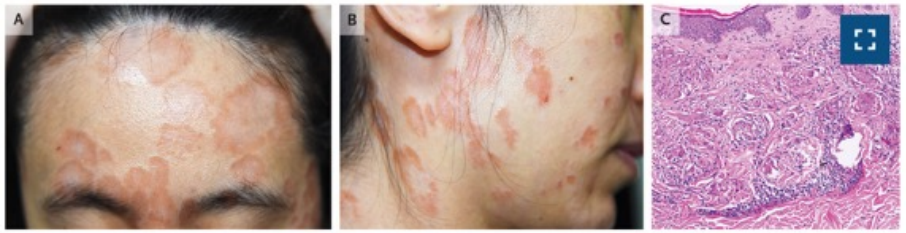
Efforts have been made to improve vaccine delivery and storage. Microneedle patches have been developed that offer the possibility of providing vaccination against measles and other conditions in remote areas where cold-chain transport is difficult. Microneedle patches also provide a pain-free, simplified method of vaccine administration. This innovation may help to improve vaccination coverage and reduce cold-chain issues. Additional randomized, controlled trials are needed to evaluate the efficacy of microneedle patches. In addition, further research on new measles vaccine candidates that can be given to younger infants is needed, because such vaccines may be required for eradication of measles.

Merkel-Cell Carcinoma



A 72-year-old woman presented to the dermatology clinic with a 3.5-month history of an enlarging, painless lump on her left cheek. Physical examination showed a dome-shaped, reddish nodule surrounded by erythema on the left cheek (Panel A). The nodule had a shiny surface and central hemorrhagic crust. A punch biopsy of the lesion revealed dermal infiltration by small, round, blue cells arranged in nests, as well as scant cytoplasm and hyperchromatic nuclei; mitoses were frequently observed (Panel B, hematoxylin and eosin stain). Immunohistochemical testing was positive for perinuclear CK20 and synaptophysin. A diagnosis of Merkel-cell carcinoma — a rare, aggressive cutaneous neuroendocrine carcinoma — was made. Merkel-cell carcinoma typically manifests as a rapidly enlarging, nontender, shiny nodule on sun-exposed skin in an older person. Risk factors include ultraviolet radiation, immunosuppression, and infection with Merkel-cell polyomavirus (testing for which was not available in this patient). Immunotherapy may be used in widespread disease, but no metastases were seen on staging imaging in this patient. Wide local excision of the lesion was performed, and sentinel lymph-node biopsy of the neck was negative. Adjuvant radiotherapy was administered to enhance local disease control. At 6 months of follow-up, no recurrence was noted.

Cutaneous Sarcoidosis with Annular Plaques



A previously healthy 38-year-old woman presented to the dermatology clinic with a 12-month history of an itchy rash that had started on her forehead and spread to her cheeks and neck. She had no shortness of breath, cough, joint pain, or eye symptoms. The physical examination was notable for multiple brownish-red annular plaques with a thinly raised border and central hypopigmentation with slight atrophy in areas on the forehead (Panel A), as well as on the cheeks and neck (Panel B). No other lesions were noted. Histopathological analysis of a skin-biopsy sample obtained from the right side of the neck showed noncaseating epithelioid granulomas with sparse lymphocytic infiltration in the superficial dermis (Panel C, hematoxylin and eosin stain). Subsequent laboratory testing was notable for a normal serum calcium level and a negative tuberculosis interferon-γ release assay. Computed tomography of the chest showed multiple tiny nodules in a perilymphatic distribution and hilar and mediastinal lymphadenopathy. A diagnosis of sarcoidosis was made. Cutaneous sarcoidosis has many manifestations, including but not limited to plaque sarcoidosis (seen here with less common annular morphologic features), papular sarcoidosis, and lupus pernio. Treatment with prednisone (at a dose of 30 mg daily) and topical tacrolimus was started. At the 3-month follow-up, the brownish-red annular plaques had lightened in color and flattened at the margins, and the findings on chest imaging had improved. The dose of prednisone was then tapered to 20 mg daily, and follow-up was continuing.

Motor Vehicle Collision Due to Left Hemineglect Associated with a Stroke

A 75-year-old man with hypertension was brought to the emergency department after a motor vehicle collision. A video recording from the dashboard camera in his car showed a sudden inability to react to events on his left side, which resulted in the crash (Panel A and videos). During the physical examination, no visual-field deficit was noted on confrontation testing. On double simultaneous stimulation of the visual fields, the patient saw the stimulus on his right side but not his left side. Tests of strength and sensation were normal. The nature of the patient's accident and the examination findings indicated hemineglect — a lack of awareness of stimuli on one side of the body that is most commonly due to the presence of a lesion in the parietal lobe on the contralateral side. Owing to his confusion, the patient could not engage in more detailed testing of neglect. Computed tomography of the head revealed a parieto-occipital subcortical hemorrhage on the right side (Panel B, axial view). Diffusion-weighted magnetic resonance imaging of the head did not show infarction in that region. A diagnosis of an acute hemorrhagic stroke resulting in left hemineglect and a motor vehicle collision was made. The patient received treatment with antihypertensive medications and underwent physical and occupational therapy. After a prolonged hospital stay, he was discharged to a rehabilitation facility with ongoing hemineglect.

VIDEO

Motor Vehicle Collision after Loss of Reaction 0m 50s

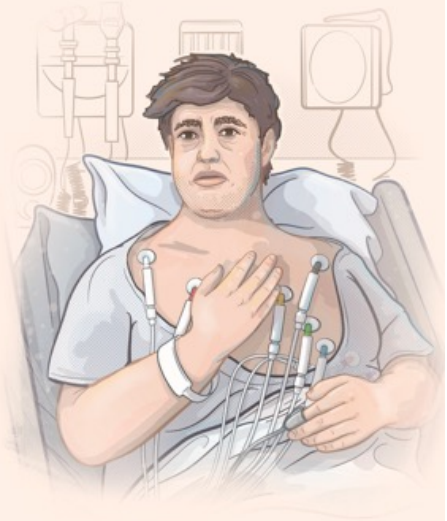
Case Presentation

A 34-year-old man presented to the hospital with exercise intolerance, night sweats, and bradycardia.

Two weeks before the current presentation, he saw his primary care physician for evaluation of myalgias and night sweats that had been present for 1 week. His symptoms had developed while he was on vacation along the Massachusetts coast and were initially accompanied by fevers that resolved within a few days. The patient's son also had a febrile illness during that time that had since resolved. His symptoms were attributed to a suspected viral illness.

On the day of presentation, the patient initially went to urgent care with persistent night sweats and new exercise intolerance. He was sent to the emergency department after he was found to have bradycardia, with a heart rate of 36 beats per minute.

On evaluation in the emergency department, the patient reported no fevers, chills, chest pain, dyspnea, palpitations, or lightheadedness. He said he did not have any sick contacts apart from his son.



Patient History

Medical History

Gastroesophageal reflux disease

Obesity

Recurrent ear infections in childhood

Medications

Omeprazole, 20 mg daily as needed for heartburn

Allergies

Amoxicillin (rash)

Social History

Drinks alcohol socially

Reports no history of tobacco or electronic cigarette use

Reports no history of illicit drug use

Lives an active lifestyle and is currently training for a marathon

Married with three children

Works in health care in Massachusetts

Family History

Paternal grandfather with atrial fibrillation and colon cancer, diagnosed at 62 years of age

Maternal uncle with prostate cancer, diagnosed in his 60s

Physical Examination

Vital signs

Temperature, 36.7°C

Heart rate, 56 beats per minute

Blood pressure, 142/80 mm Hg

Respiratory rate, 18 breaths per minute

Oxygen saturation, 99% while the patient was breathing ambient air

General appearance

Well-appearing

Neck

Trachea at midline

No thyromegaly

No cervical lymphadenopathy

Heart

Bradycardia with an irregular rhythm

No murmurs, rubs, or gallops

Jugular venous pulsation not visualized

Lungs

Clear on auscultation

No wheezes, rhonchi, or rales

Abdomen

Soft, nondistended, and nontender on palpation

Normoactive bowel sounds

Arms and legs

Warm and well-perfused

No edema

Skin

No rashes or lesions

Nervous system

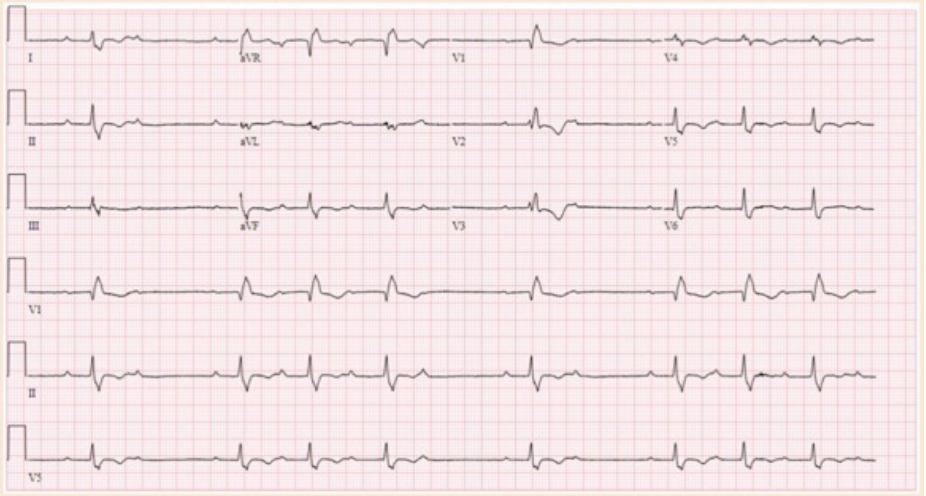
Grossly normal motor function

Awake, alert, and able to answer questions

No Brudzinski or Kernig signs

Electrocardiogram (ECG)

ECG on presentation was notable for sinus bradycardia with Mobitz type I second-degree atrioventricular (AV) block as well as right bundle-branch block (RBBB). No previous ECGs were available for comparison.



Laboratory Evaluation

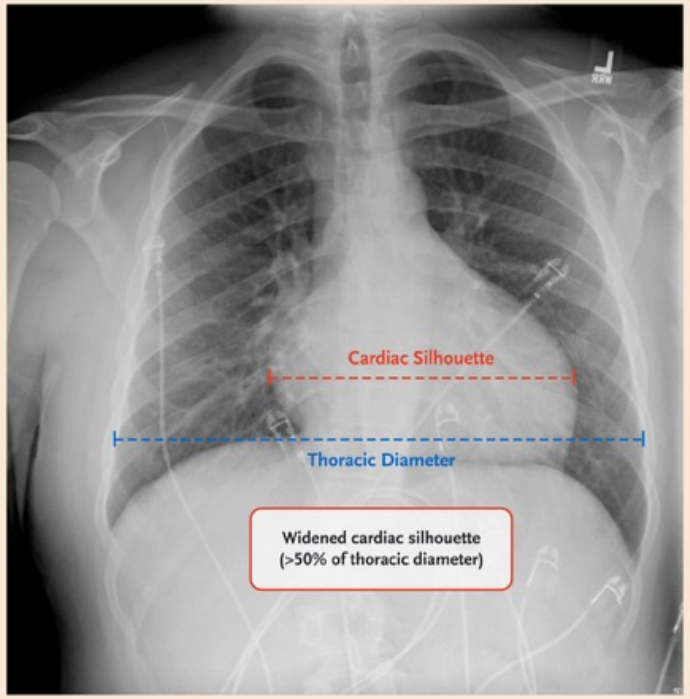
The results of laboratory testing are shown below.

Variable*	Result	Normal Range	Flag
Sodium (mmol/liter)	140	136–142	–
Potassium (mmol/liter)	4.5	3.5–5.0	–
Chloride (mmol/liter)	102	98–108	–
Bicarbonate (mmol/liter)	25	23–32	–
Urea nitrogen (mg/dl)	20	9–25	–
Creatinine (mg/dl)	0.76	0.70–1.30	–
Estimated glomerular filtration rate (ml/min/1.73 m^2)	>120	>60	–
Glucose (mg/dl)	101	70–100	High
High-sensitivity troponin T (ng/liter)	<6	0–14	–
Thyrotropin (μIU/ml)	1.81	0.50–5.70	–
White-cell count (per mm^3)	6040	4000–10,000	–
Neutrophils (%)	64.2	48.0–76.0	–
Hematocrit (%)	41.3	36.0–48.0	–
Hemoglobin (g/dl)	13.8	11.5–16.4	–
Platelet count (per mm^3)	237,000	150,000–450,000	–
Prothrombin time (sec)	13.2	12.0–14.4	–
SARS-CoV-2 RNA on PCR testing	Not detected	Not detected	–
RSV on PCR testing	Negative	Negative	–
Influenza A virus on PCR testing	Negative	Negative	–
Influenza B virus on PCR testing	Negative	Negative	–

* PCR denotes polymerase-chain-reaction, RSV respiratory syncytial virus, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

Chest Radiography

A posterior–anterior plain radiograph of the chest obtained on presentation showed a widened cardiac silhouette and no abnormalities in the lung fields.



What Would You Do?

Which one of the following strategies is appropriate at this time?

Select a strategy to see whether it is an appropriate choice and to learn about the probable outcome. You will be able to return to the list of choices to review the probable consequences of each choice.

- A Admit the patient to the hospital for placement of a permanent pacemaker
- B Discharge the patient with a referral for outpatient cardiology follow-up
- C Admit the patient to the hospital for continuous ECG monitoring and additional testing
- D Immediately administer atropine
- E Admit the patient to the hospital for coronary angiography

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- A Admit the patient to the hospital for placement of a permanent pacemaker ✗
- B Discharge the patient with a referral for outpatient cardiology follow-up ✗
- C Admit the patient to the hospital for continuous ECG monitoring and additional testing ✓
- D Immediately administer atropine ✗
- E Admit the patient to the hospital for coronary angiography ✗

Atrioventricular (AV) Block

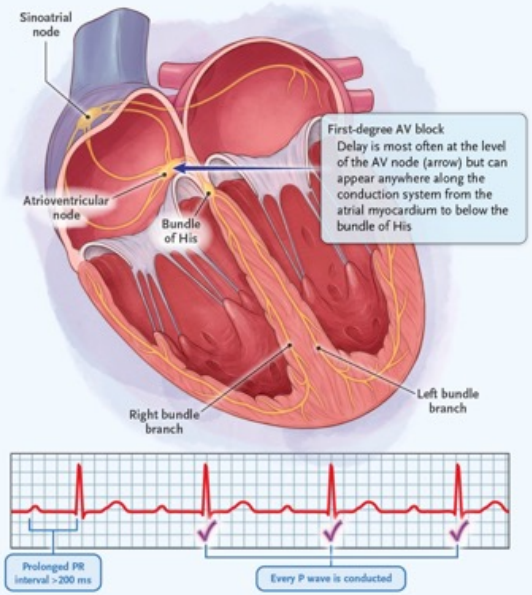
LEARNING MODULE

Classification

Select an AV block type to see the definition, the location of the block, and the ECG findings.

- (●) First-degree AV block
- ( ) Mobitz type I second-degree AV block
- ( ) Mobitz type II second-degree AV block
- ( ) Third-degree AV block (complete heart block)

Defined by a prolonged PR interval of >200 milliseconds without loss of atrioventricular conduction (i.e., every P wave is followed by a QRS complex). It represents delayed AV conduction rather than a true "block."



Further Laboratory Evaluation

The patient was admitted to the hospital for continuous ECG monitoring and additional workup. Given that Lyme disease is endemic in Massachusetts, where the patient lives, and can cause heart block, further diagnostic studies were obtained. In addition to modified two-tiered serologic testing for Lyme disease (combined IgG–IgM screening immunoassay followed by separate immunoassays for IgG and IgM for confirmation), the patient was screened for babesiosis and anaplasmosis because these diseases are transmitted in the northeastern United States by the same species of tick, *Ixodes scapularis*.

Variable	Result	Normal Range	Flag
Lyme antibody screen	Positive	Negative	Abnormal
Lyme IgG	Positive	Negative	Abnormal
Lyme IgM	Positive	Negative	Abnormal
Thin blood parasite smear	No parasites seen	No parasites seen	–
Thick blood parasite smear	No parasites seen	No parasites seen	–
Babesia on PCR testing	No parasites seen	No parasites seen	–
Anaplasma on PCR testing	No parasites seen	No parasites seen	–
Ehrlichia on PCR testing	No parasites seen	No parasites seen	–

What Would You Do Next?

The patient's clinical presentation and positive serologic tests for Lyme disease were consistent with the diagnosis of Lyme carditis.

Which one of the following strategies represents a preferred treatment for this patient? Select a strategy to see whether it is an appropriate choice for treatment and to learn about the probable outcome. You will be able to return to the list of choices to review the probable consequences of each choice.

- A. Administer a 21-day course of oral doxycycline ✗
- B. Administer a 21-day course of intravenous ceftriaxone ✓
- C. Administer intravenous ceftriaxone and then transition to oral doxycycline once conduction improves, for a 14-day total course ✓

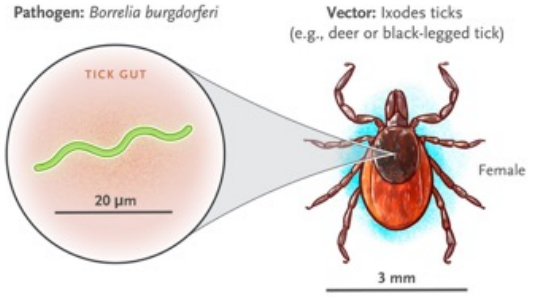
Administering intravenous ceftriaxone with a transition to oral doxycycline once conduction improves, for a 14-day total course of antibiotics, is an appropriate treatment choice.

Outcome

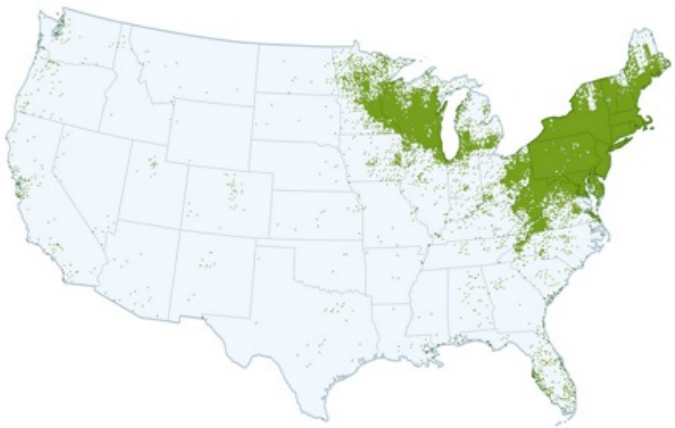
The patient's AV block abates within 72 hours after starting therapy, with the return of 1:1 AV conduction. On hospital day 4, he is transitioned to oral doxycycline, for a 14-day total course of antibiotics. He is discharged home on hospital day 5. A 2-week external patch monitor confirms the resolution of his AV block.

Comments

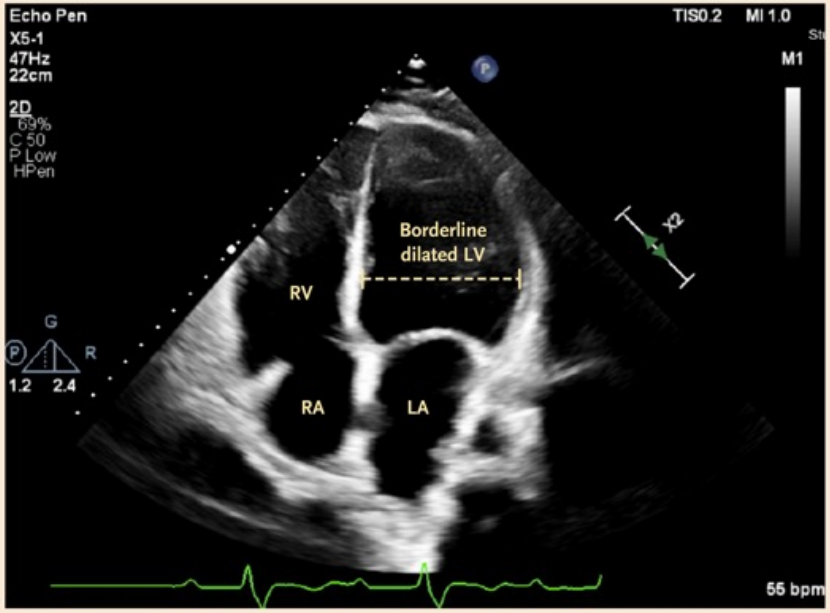
Initiation of antibiotics is a critical component of the management of this patient's Lyme carditis and AV block, and intravenous ceftriaxone is the appropriate initial therapy. The 2020 Infectious Diseases Society of America–American Academy of Neurology–American College of Rheumatology Lyme disease guidelines state that patients can be transitioned to oral antibiotics once there is evidence of improved conduction. Doxycycline, amoxicillin, cefuroxime axetil, and azithromycin are oral antibiotic options for Lyme carditis.



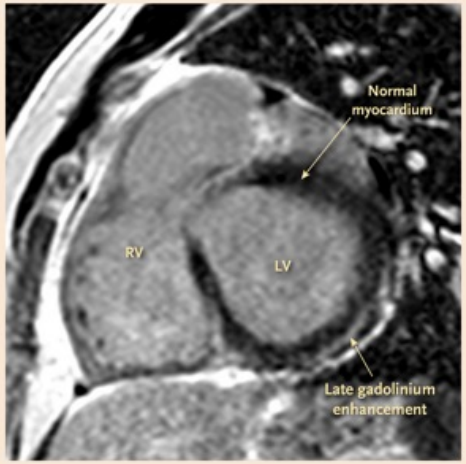
U.S. Lyme Disease Cases Reported to the CDC (2023)

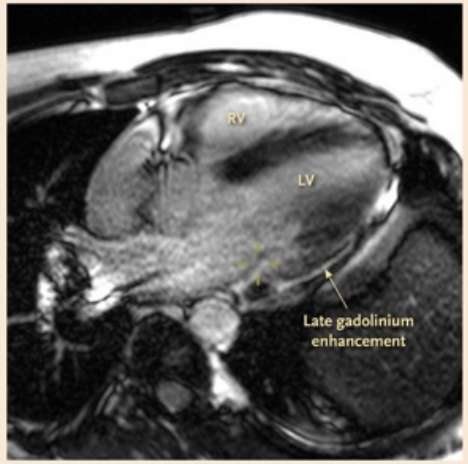


Source: Data are from the Centers for Disease Control and Prevention



Given that in addition to AV block, the patient had RBBB, a finding less commonly associated with Lyme carditis, the decision was made to perform cardiac magnetic resonance imaging (MRI) to assess for an inflammatory process or scar.





Findings on cardiac MRI were consistent with myocarditis with diffuse myocardial inflammation and a focus of recent injury in the epicardial inferolateral wall, as evidenced by late gadolinium enhancement.

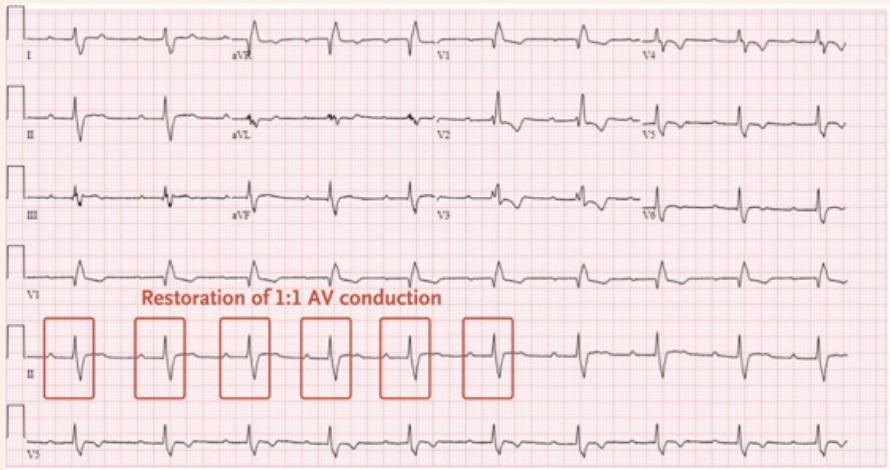
Given the patient's lack of prior cardiac history and risk factors and the pattern of late gadolinium enhancement on cardiac MRI, the LV dilatation seen on the echocardiogram is probably explained by myocarditis. No previous imaging was available to assess the chronicity of the LV dilatation.

Outcome and Management

Hospital

Day 3

Mobitz type I second-degree AV block resolved, with restoration of 1:1 AV conduction.



Day 4

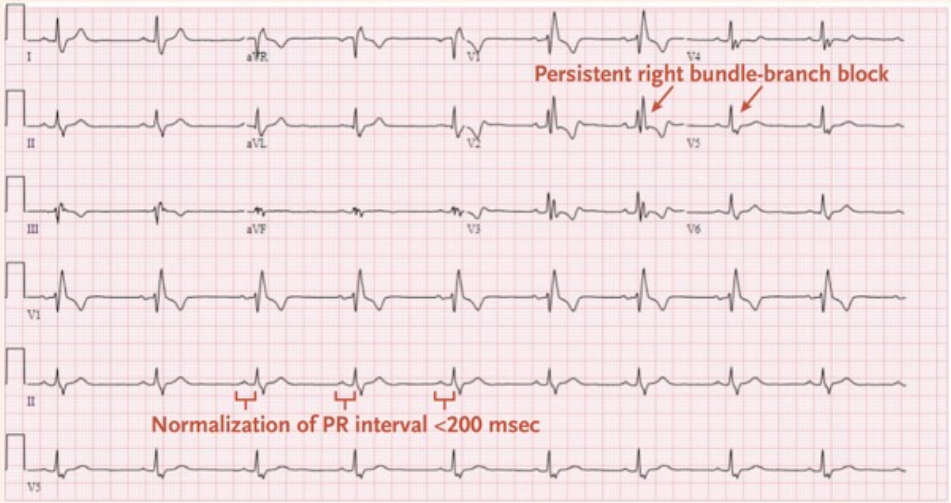
Given sustained improvement in conduction, the patient was transitioned from intravenous ceftriaxone to oral doxycycline with a plan for a 14-day total course of antibiotics.

Day 5

The patient was discharged with a 2-week heart rhythm monitor, and cardiology follow-up was arranged.

Cardiology Follow-up 1 Month after Discharge

A 14-day heart rhythm monitor showed no evidence of recurrence of Mobitz type I second-degree AV block. ECG performed in the office showed resolution of AV block but persistent RBBB. It is possible that the patient's RBBB predated his Lyme carditis, but no previous ECGs were available to make this determination.



The patient reported feeling well, without recurrence of symptoms.

Teaching Points

- AV block refers to delayed, inconsistent, or absent conduction between the atria and the ventricles and has several possible causes.
- Lyme carditis should be considered in all patients presenting with new AV block in areas where the disease is endemic (or after travel to such areas), even in the absence of preceding erythema migrans.
- The AV block associated with Lyme carditis generally resolves with appropriate antibiotic therapy, and placement of a permanent pacemaker is not indicated.
- Advanced cardiac imaging can be a useful tool in the evaluation of conduction abnormalities.

Case 36-2025: A 55-Year-Old Woman with Dyspnea, Fatigue, and Gastrointestinal Bleeding

A 55-year-old woman was admitted to this hospital because of recurrent rectal bleeding and shortness of breath.

The patient had been in her usual state of health until 6 months before the current presentation, when hematochezia developed. She was evaluated at the emergency department of another hospital. The hemoglobin level was 8.0 g per deciliter (reference range, 12.0 to 16.0), with a normal mean corpuscular volume; the white-cell count and platelet count were normal. The patient was admitted to the hospital, and colonoscopy was performed; internal hemorrhoids were detected, but no masses, ulcers, or polyps were noted. Treatment with oral iron was initiated, and she was discharged home.

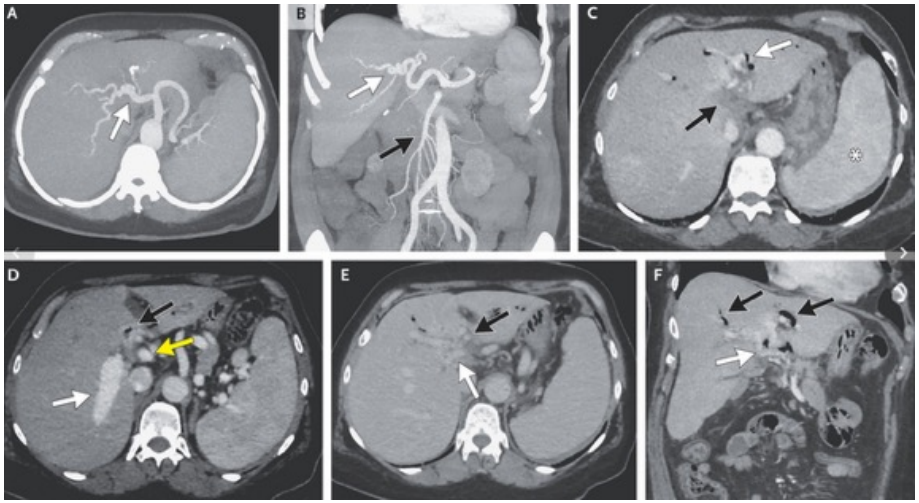
Three months before the current presentation, hematochezia developed again, and the patient presented to the emergency department of a second hospital. The hemoglobin level was 6.4 g per deciliter, with a mean corpuscular volume of 73 fl (reference range, 80 to 100). The white-cell count was 3700 per microliter (reference range, 4000 to 11,000), and the platelet count was normal. The ferritin level was 5 µg per liter (reference range, 10 to 200), and the transferrin saturation was 3% (reference range, 14 to 50). The patient was admitted to the second hospital. Two units of packed red cells were transfused, and an intravenous infusion of iron was administered.

Esophagogastroduodenoscopy (EGD) with additional enteroscopy reportedly showed a normal-appearing esophagus, stomach, and duodenum. Owing to the patient's anatomy, only the proximal jejunum could be seen and its appearance was normal; no blood was noted in the gastrointestinal tract. The rectal bleeding abated spontaneously, and the patient was discharged home.

Two weeks later, the patient was evaluated in the outpatient gastroenterology clinic of the second hospital. Video-capsule endoscopy was reportedly negative. Given the negative endoscopic evaluation, treatment with scheduled iron infusions was started.

Two months before the current presentation, the patient had recurrent hematochezia, along with fatigue, prompting her to present to the emergency department of this hospital. The vital signs were normal, and the hemoglobin level was 6.8 g per deciliter, which led to admission to this hospital. Results of serum protein electrophoresis were normal, as were the serum levels of free kappa and free lambda light chains. The blood levels of copper, lead, and zinc were also normal. One unit of packed red cells was transfused, and intravenous iron was administered, which resulted in a decrease in symptoms. Given the recent negative endoscopic evaluation and the absence of ongoing rectal bleeding, further investigation was deferred, and the patient was discharged home with instructions to return to her gastroenterologist for follow-up care.

Computed tomography (CT) with angiography was performed according to a gastrointestinal bleeding protocol that was specific to the abdomen and pelvis. No active gastrointestinal bleeding was identified on imaging. The celiac and mesenteric arterial vasculature was normal, including a patent hepatic artery and superior mesenteric artery (Figure 1A and 1B). There was occlusion of the left portal vein with restoration of flow in the distal segment (Figure 1C). The right portal vein was dilated, and stenosis was present at the junction of the right portal vein and the main portal vein, which was patent (Figure 1D and 1E). Associated splenomegaly was noted, along with portosystemic collaterals in the hepatic hilum. The study also showed evidence of a previous hepaticojejunostomy in the hepatic hilum surrounded by the collaterals and the presence of expected pneumobilia associated with hepaticojejunostomy (Figure 1F).



CT Angiography.

CT angiography was performed to evaluate for active gastrointestinal bleeding. An axial maximum-intensity-projection (MIP) image obtained in the early arterial phase (Panel A) shows a patent hepatic artery (arrow) at the level of the celiac axis. A coronal MIP image obtained in the early arterial phase (Panel B) shows the patent hepatic artery (white arrow) and a patent superior mesenteric artery (black arrow). An axial image obtained in the late arterial phase (Panel C) shows occlusion of the left portal vein (black arrow) with distal reconstitution (white arrow) and splenomegaly (asterisk). A more inferior axial image (Panel D) shows a dilated right portal vein (white arrow), a patent main portal vein (black arrow), and portosystemic collaterals in the hepatic hilum (yellow arrow). A superior axial image (Panel E) shows stenosis at the junction of the right portal vein and the main portal vein (white arrow) and additional portosystemic collaterals (black arrow). A coronal image at the level of the hepatic hilum (Panel F) shows evidence of a previous hepaticojejunostomy surrounded by portosystemic collaterals (white arrow) and the presence of expected pneumobilia in the left and right hepatic lobes (black arrows).

The patient's medical history was notable for seronegative ocular myasthenia gravis and symptomatic premature ventricular complexes, for which she had undergone cardiac ablation. Surgical history was notable for cholecystectomy, which had been performed 20 years before the current presentation; the procedure had been complicated by laceration of the bile duct, for which she had undergone open repair and hepaticojejunostomy. Appendectomy had been performed 4 years before the current presentation. The patient took no medications. She did not take nonsteroidal antiinflammatory drugs or dietary supplements. She had no known adverse reactions to medications. She lived in Massachusetts with her husband and adult child. She did not smoke, drink alcohol, or use recreational drugs. She was a retired educator. She reported no recent travel and had not lived outside the United States. She had no family history of liver disease, bleeding disorders, or cancer.

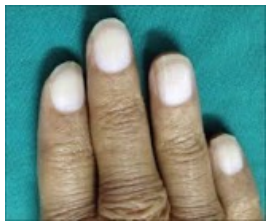
The oral temperature was 36.1°C, the blood pressure 99/55 mm Hg, the heart rate 61 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. The weight was 85 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 30. On examination, the skin was pale but not jaundiced. The abdomen was soft and nontender, without distention or palpable organomegaly. She did not have Terry's nails, spider angiomas, or palmar erythema.

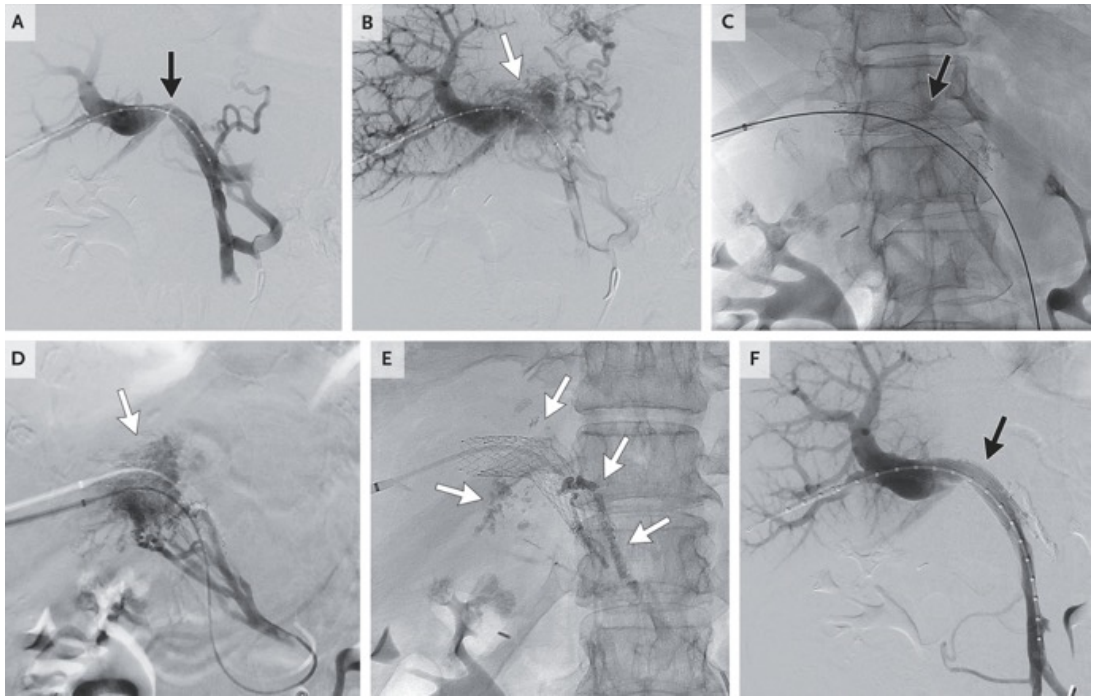
Variable	Reference Range, Adults†	2 Mo before Current Presentation	On Current Presentation
Hemoglobin (g/dl)	12.0–16.0	6.8	6.5
Hematocrit (%)	41.0–53.0	23.5	32.2
White-cell count (per μl)	4500–11,000	5490	3170
Differential count (per μl)			
Absolute neutrophils	1800–7700	3460	1610
Absolute lymphocytes	1000–4800	1510	1270
Absolute monocytes	200–1200	390	190
Absolute eosinophils	0–900	90	70
Absolute basophils	0–300	20	20
Immature granulocytes	0–100	0	0
Platelet count (per μl)	150,000–400,000	167,000	144,000
Mean corpuscular volume (fl)	80–100	83	86
Sodium (mmol/liter)	135–145	141	141
Potassium (mmol/liter)	3.4–5.0	4.1	3.7
Chloride (mmol/liter)	98–108	108	108
Carbon dioxide (mmol/liter)	23–32	23	25
Urea nitrogen (mg/dl)	8–25	12	17
Creatinine (mg/dl)	0.60–1.50	0.68	0.60
Calcium (mg/dl)	8.5–10.5	8.7	9.0
Glucose (mg/dl)	70–110	86	108
Aspartate aminotransferase (U/liter)	10–40	22	27
Alanine aminotransferase (U/liter)	10–55	33	30
Alkaline phosphatase (U/liter)	15–115	91	83
Total bilirubin (mg/dl)	0.0–1.2	0.3	0.2
Albumin (g/dl)	3.3–5.0	4.2	3.8
Globulin (g/dl)	1.9–4.1	2.7	2.6
Lead (μg/dl)	0.0–3.5	<1.0	—
Copper (μg/dl)	77–206	142	—
Zinc (μg/dl)	60–106	62	—
IgG (mg/dl)	614–1295	828	—
IgA (mg/dl)	69–309	207	—
IgM (mg/dl)	53–334	78	—
Free kappa light chain (mg/liter)	3.3–19.4	15.4	—
Free lambda light chain (mg/liter)	5.7–26.3	14.3	—
Kappa:lambda ratio	0.3–1.7	1.08	—
Serum protein electrophoresis	Negative for monoclonal component	Negative for monoclonal component	—
Prothrombin time (sec)	9.4–12.5	14.8	13.9
International normalized ratio	0.8–1.1	1.3	1.2

Determining the Source of Blood Loss

After initial stabilization, the next step in the management of gastrointestinal bleeding is to determine the source of blood loss. The color of the stool can provide insight into the general location of gastrointestinal bleeding. This patient initially presented with hematochezia, the passage of red blood in the stool, which is indicative of either a lower gastrointestinal hemorrhage or a brisk episode of upper gastrointestinal bleeding. The subsequent occurrence of rectal bleeding that was described as melena is consistent with an upper gastrointestinal source, although bleeding in the proximal colon can also cause melena. Since this patient had passed both stool containing red blood and melena, the location of the bleeding is most likely in the upper gastrointestinal tract. Furthermore, the presence of both gastrointestinal hemorrhage and thrombocytopenia prompts consideration of underlying portal hypertension. In the context of portal hypertension, thrombocytopenia can occur as a result of splenic sequestration of platelets and, in persons with chronic liver disease, decreased thrombopoietin production. In this patient, the finding of thrombocytopenia is particularly notable because reactive thrombocytosis often occurs in the context of iron-deficiency anemia.

Terry's Nails sind eine Nagelveränderung, bei der die Nägel fast vollständig weiß erscheinen („Milchglas-Erscheinung“) und nur an der Spitze einen schmalen, rot-braunen Streifen haben, der das Mondfeld verdeckt. Sie sind oft ein Hinweis auf Leberzirrhose, Herzinsuffizienz, Nierenversagen oder Diabetes, können aber auch durch normales Altern oder Mangelernährung verursacht werden und erfordern eine ärztliche Abklärung, um die zugrunde liegende Ursache zu behandeln.





Interventional Radiology Imaging Studies.

An early-phase portal venogram (Panel A) shows severe stenosis of the portal vein (arrow), and a delayed-phase portal venogram (Panel B) shows filling of cavernomas and jejunal varices (arrow). A fluoroscopic image (Panel C) shows placement of a self-expanding bare-metal stent across the portal-vein stenosis (arrow). Selective venograms show the jejunal varices (Panel D, arrow), followed by embolization of the jejunal varices with the use of *N*-butyl-2-cyanoacrylate (Panel E, arrows). A postembolization portal venogram shows a patent portal-vein stent (Panel F, arrow) with in-line portal flow from the superior mesenteric vein into the intrahepatic portal veins and elimination of jejunal variceal filling after embolization.

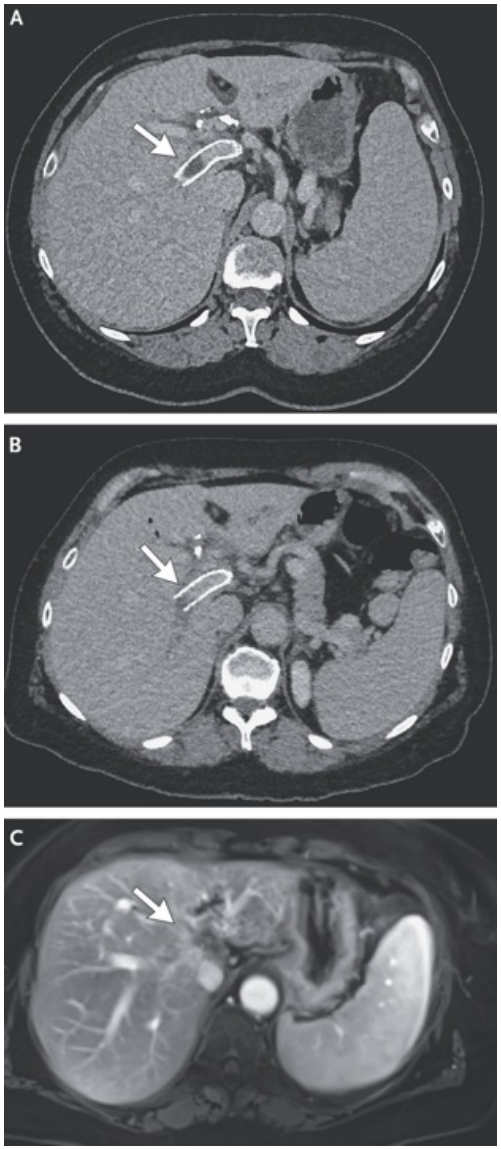
Radiologic Diagnosis

Portal-vein stenosis causing postsurgical jejunal variceal bleeding at the level of the hepaticojejunostomy site.

Follow-up

On the night of the stenting procedure, fever developed, which was attributed to postembolization syndrome, given that no clinical signs of infection (other than fever) were present, no growth was seen on blood cultures, and there was no evidence of pneumonia on chest radiography. The day after the procedure, the hemoglobin level was 6.7 g per deciliter, and 1 unit of packed red cells was transfused. The hemoglobin level subsequently increased to 8.7 g per deciliter. Over the course of the next few days, the patient's melena abated. She was discharged home 4 days after the procedure.

CT angiography of the abdomen performed 18 days after the stenting procedure showed a nonocclusive thrombus in the distal end of the portal-vein stent (Figure 4A). Thrombus formation in this location was thought to be associated with a size mismatch between the stent and the poststenotic dilatation of the portal vein, resulting in turbulent flow. At this time, the patient's gastrointestinal bleeding had not recurred; thus, a decision was made to start treatment with apixaban for the thrombus associated with the stent.



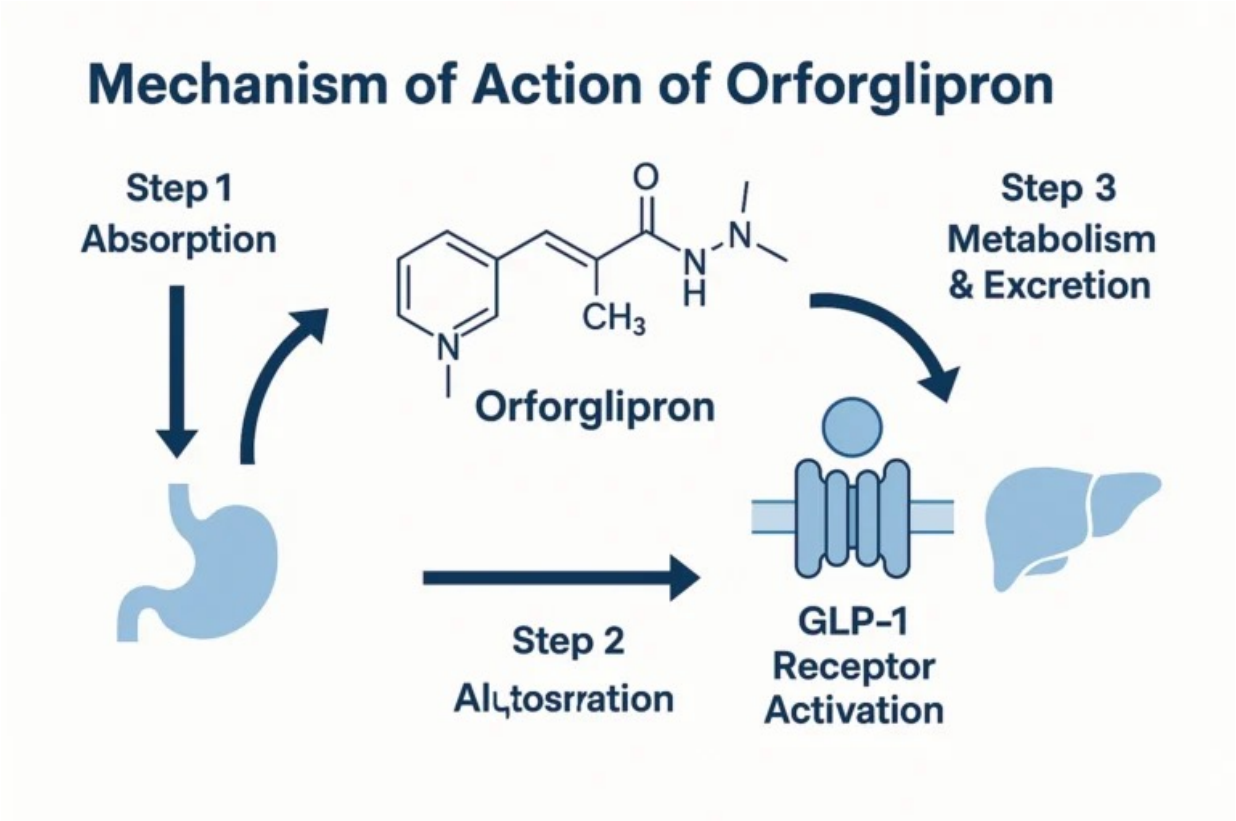
Two months after the stenting procedure, follow-up CT angiography showed a decrease in the extent of the thrombus and a patent portal-vein stent (Figure 4B). Four months after the procedure, the hemoglobin level was 12.4 g per deciliter. The patient was able to continue anticoagulant therapy without bothersome side effects, and she had had no further episodes of gastrointestinal bleeding. MRCP performed 5 months after the procedure (Figure 4C) showed a radiologically significant decrease in perihilar hepatic enhancement, which indicated decreased filling of the varices near the hepaticojejunostomy site. This finding is not consistent with a hilar neoplasm as the cause of her portal-vein occlusion.

Does it seem odd that this marked portal-vein bleeding commenced briskly and suddenly after so many decades if the bleeding was due to benign postsurgical changes?

It is undoubtedly an unusual aspect of the case. This may have been a situation in which years of remodeling in the vasculature led to gradual rises in portal pressure until a critical point was reached. An analogy can be drawn to many patients with cirrhosis and portal hypertension who can have subclinical portal hypertensive complications, such as varices, for years until a decompensation point is reached and frequent bleeding ensues.

The degree of portal stenosis over time was also unknown, given that we did not have any previous cross-sectional imaging findings. Thus, it is unclear whether the portal stenosis worsened over time in the context of fibrotic remodeling, which could have contributed to a more progressive manifestation of her portal hypertension.

Orforglipron ist ein neuer, oral einzunehmender (als Tablette) GLP-1-Rezeptoragonist von Eli Lilly, der zur Behandlung von Adipositas und Typ-2-Diabetes entwickelt wird und eine Alternative zu den beliebten Abnehmspritzen darstellt. Er ahmt das körpereigene Hormon GLP-1 nach, was zu schnellerer und länger anhaltender Sättigung führt und den Appetit zügelt. Studien zeigen signifikante Gewichtsabnahme und Blutzuckerverbesserung, mit Plänen für Zulassungsanträge Ende 2025.



Orforglipron, an oral small-molecule GLP-1 receptor agonist, for the treatment of obesity in people with type 2 diabetes (ATTAIN-2): a phase 3, double-blind, randomised, multicentre, placebo-controlled trial

Summary

Background Obesity is a chronic disease that significantly contributes to type 2 diabetes and its complications. We aimed to evaluate orforglipron, an oral small-molecule (non-peptide) GLP-1 receptor agonist, for obesity treatment in adults with type 2 diabetes.

Methods This 72-week, phase 3, double-blind, placebo-controlled trial was conducted across 136 sites in ten countries. Participants with a BMI of 27 kg/m² or higher and glycated haemoglobin (HbA_{1c}) of 7–10% (53–86 mmol/mol) were randomly assigned (1:1:1:2) to once-daily orforglipron 6 mg, 12 mg, 36 mg, or placebo. The primary endpoint was the mean percent change in bodyweight from baseline to week 72. The treatment regimen estimand (using data from all randomly assigned participants, regardless of intercurrent events) was the primary estimand, with the efficacy estimand considered supportive. Safety was assessed in all patients who received at least one dose of study drug. This trial was registered at ClinicalTrials.gov (NCT05872620) and is completed.

Findings From June 5, 2023, to Feb 15, 2024, 2859 participants were screened, and 1613 (757 [46·9%] female) were randomly assigned, following a dose-escalation phase, to receive orforglipron 6 mg (n=329), 12 mg (n=332), 36 mg (n=322), or placebo (n=630), as an adjunct to lifestyle modification; 1444 (89·5%) completed the study. Baseline bodyweight was 101·4 kg (SD 22·5), BMI 35·6 kg/m² (SD 6·6), and HbA_{1c} 8·05% (SD 0·75; 64·4 mmol/mol [SD 8·2]). For the treatment regimen estimand, the mean percent change in bodyweight from baseline to week 72 was –5·1% (95% CI –6·0 to –4·2) with 6 mg (estimated treatment difference [ETD] –2·7 [95% CI –3·7 to –1·6]; p<0·0001), –7·0% (–7·8 to –6·2) with 12 mg (ETD –4·5 [–5·5 to –3·6]; p<0·0001), and –9·6% (–10·5 to –8·7) with 36 mg orforglipron (ETD –7·1 [–8·2 to –6·1]; p<0·0001), versus –2·5% (–3·0 to –1·9) with placebo (all p<0·0001 compared with placebo). All prespecified weight and cardiometabolic measures including HbA_{1c} statistically significantly improved with orforglipron. Treatment discontinuations due to adverse events (mainly gastrointestinal-related) were higher for orforglipron (6·1–9·9%) versus placebo (4·1%). The most common adverse events with orforglipron were mild-to-moderate gastrointestinal events, predominantly occurring during dose escalation. Ten deaths were reported during the study: six with orforglipron and four with placebo. Investigators deemed all deaths unrelated to the study treatment, except for one case in the placebo group and one case in the 12 mg orforglipron group. For the case in the orforglipron group, no treatment-related association was reported.

Interpretation In adults with obesity or overweight and type 2 diabetes, statistically superior reduction in bodyweight compared with placebo was demonstrated by once-daily orforglipron as an adjunct to lifestyle modification, with a safety profile similar to other GLP-1 receptor agonists.

Funding Eli Lilly and Company.

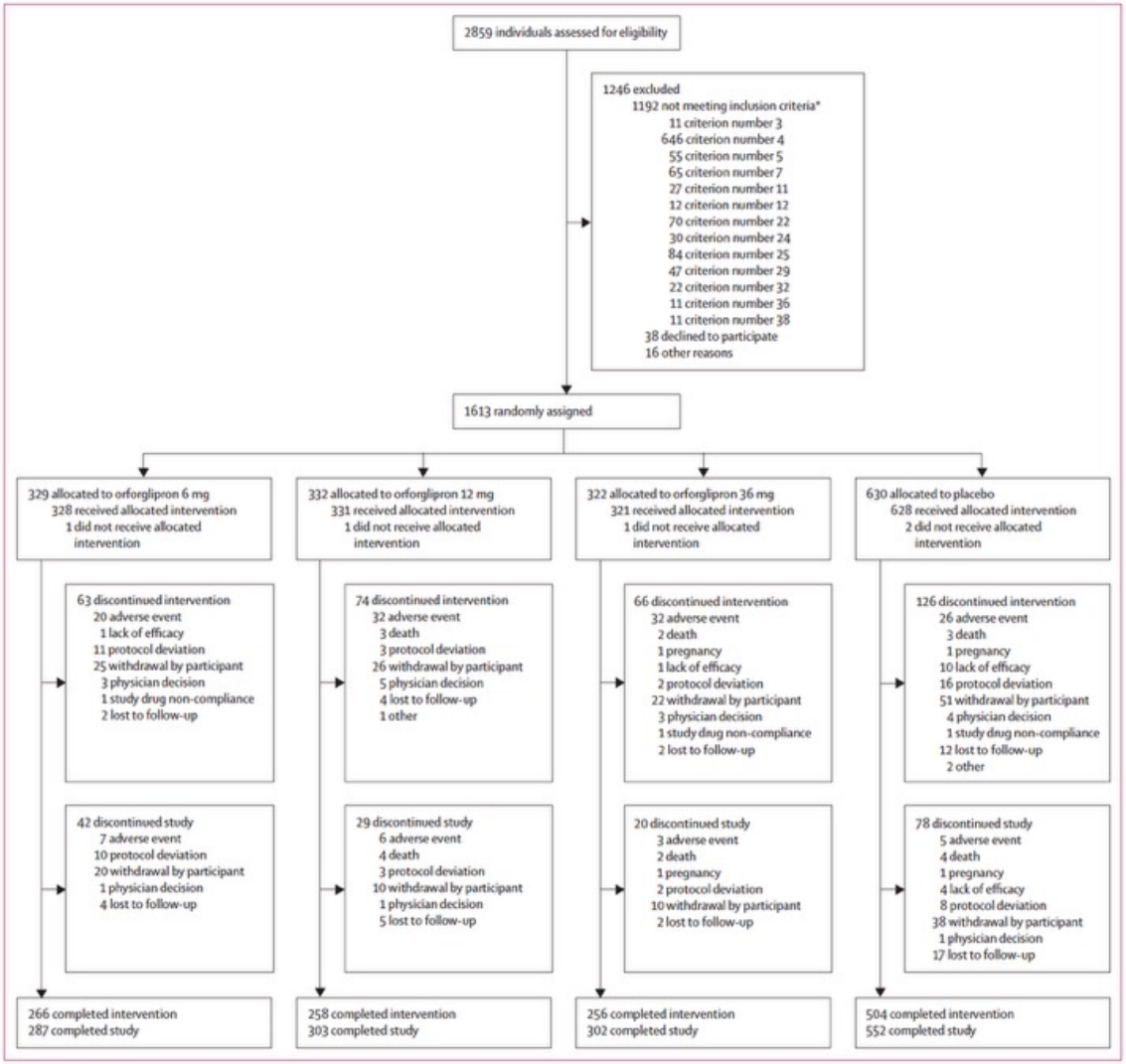


Figure 1: Trial profile

*Individual numbers are shown for inclusion criteria with n>10. For full details on the inclusion criteria and the complete list refer to the appendix (pp 11–15).

	Orforglipron 6 mg (n=329)	Orforglipron 12 mg (n=332)	Orforglipron 36 mg (n=322)	Placebo (n=630)	Total (n=1613)
Age, years	56·8 (10·4)	56·2 (10·5)	58·1 (10·8)	56·5 (10·9)	56·8 (10·7)
Age <65 years	251 (76·3%)	247 (74·4%)	221 (68·6%)	474 (75·2%)	1193 (74·0%)
Age ≥65 years	78 (23·7%)	85 (25·6%)	101 (31·4%)	156 (24·8%)	420 (26·0%)
Sex					
Female	150 (45·6%)	155 (46·7%)	154 (47·8%)	298 (47·3%)	757 (46·9%)
Male	179 (54·4%)	177 (53·3%)	168 (52·2%)	332 (52·7%)	856 (53·1%)
Race*					
American Indian or Alaska Native	0	2 (0·6%)	1 (0·3%)	2 (0·3%)	5 (0·3%)
Asian	58 (17·6%)	55 (16·6%)	54 (16·8%)	112 (17·8%)	279 (17·3%)
Black or African American	21 (6·4%)	19 (5·7%)	28 (8·7%)	37 (5·9%)	105 (6·5%)
White	238 (72·3%)	235 (70·8%)	228 (70·8%)	442 (70·2%)	1143 (70·9%)
Native Hawaiian or other Pacific Islander	2 (0·6%)	1 (0·3%)	0	3 (0·5%)	6 (0·4%)
Multiple	5 (1·5%)	12 (3·6%)	6 (1·9%)	22 (3·5%)	45 (2·8%)
Ethnicity*					
Hispanic or Latino	102 (31·0%)	95 (28·6%)	97 (30·1%)	194 (30·8%)	488 (30·3%)
Not Hispanic or Latino	221 (67·2%)	229 (69·0%)	218 (67·7%)	416 (66·0%)	1084 (67·2%)
Geographical region					
Asia	52 (15·8%)	50 (15·1%)	50 (15·5%)	102 (16·2%)	254 (15·7%)
Australia	18 (5·5%)	19 (5·7%)	20 (6·2%)	35 (5·6%)	92 (5·7%)
Central and South America	77 (23·4%)	80 (24·1%)	76 (23·6%)	150 (23·8%)	383 (23·7%)
Europe	92 (28·0%)	93 (28·0%)	87 (27·0%)	170 (27·0%)	442 (27·4%)
North America	90 (27·4%)	90 (27·1%)	89 (27·6%)	173 (27·5%)	442 (27·4%)
Duration of obesity, years	17·5 (7·6–26·1)	14·8 (7·8–23·8)	15·7 (8·5–24·1)	16·1 (8·0–24·8)	15·9 (8·0–24·6)
Duration of diabetes, years	7·6 (3·8–13·7)	6·4 (3·5–10·1)	7·0 (4·0–13·1)	6·8 (3·5–10·9)	6·9 (3·7–11·7)
Bodyweight, kg	102·3 (22·7)	102·7 (21·3)	99·8 (23·0)	101·2 (22·6)	101·4 (22·5)
BMI, kg/m²	35·9 (7·0)	36·1 (6·3)	35·1 (6·5)	35·5 (6·5)	35·6 (6·6)
BMI category					
<30 kg/m²	67 (20·4%)	52 (15·7%)	83 (25·8%)	124 (19·7%)	326 (20·2%)
≥30 to <35 kg/m²	108 (32·8%)	111 (33·4%)	97 (30·1%)	222 (35·2%)	538 (33·4%)
≥35 to <40 kg/m²	85 (25·8%)	90 (27·1%)	83 (25·8%)	151 (24·0%)	409 (25·4%)
≥40 kg/m²	69 (21·0%)	79 (23·8%)	59 (18·3%)	133 (21·1%)	340 (21·1%)
Waist circumference, cm	116·8 (15·1)	116·2 (13·4)	114·7 (15·1)	115·0 (14·6)	115·6 (14·6)
Blood pressure, mm Hg					
Systolic	131·3 (14·7)	132·1 (15·0)	132·5 (13·7)	130·6 (14·1)	131·4 (14·4)
Diastolic	81·6 (10·4)	82·1 (10·0)	81·8 (10·1)	81·0 (9·1)	81·5 (9·8)
Pulse, bpm	75·9 (11·4)	73·7 (10·7)	74·6 (10·5)	74·2 (10·5)	74·5 (10·8)
Lipid parameters, mg/dL					
Total cholesterol	167·9 (25·3)	167·1 (26·0)	167·6 (27·4)	167·5 (26·2)	167·5 (26·2)
Non-HDL cholesterol	120·7 (36·0)	121·4 (34·7)	121·2 (37·4)	122·3 (35·4)	121·6 (35·7)
HDL cholesterol	43·5 (25·7)	42·8 (23·8)	43·1 (25·1)	42·0 (25·8)	42·7 (25·3)
LDL cholesterol	84·3 (47·5)	83·8 (45·3)	85·5 (50·0)	84·6 (49·3)	84·5 (48·2)
Triglycerides	157·4 (57·2)	164·4 (53·3)	157·2 (52·1)	162·8 (53·5)	160·9 (53·9)
eGFR†, mL/min per 1·73 m²	82·3 (20·9)	83·9 (21·0)	82·2 (22·5)	82·7 (21·5)	82·8 (21·5)
HbA_{1c}, %	8·03 (0·73)	8·08 (0·76)	8·05 (0·73)	8·03 (0·75)	8·05 (0·75)
HbA_{1c}, mmol/mol	64·3 (8·0)	64·8 (8·4)	64·5 (8·0)	64·3 (8·2)	64·4 (8·2)
Fasting serum glucose, mg/dL	152·9 (41·6)	155·1 (43·0)	154·7 (40·1)	151·5 (39·5)	153·1 (40·8)
Fasting serum glucose, mmol/L	8·5 (2·3)	8·6 (2·4)	8·6 (2·2)	8·4 (2·2)	8·5 (2·3)
Fasting insulin, mIU/L	18·9 (75·6)	19·7 (65·9)	18·8 (76·0)	18·2 (71·7)	18·8 (72·2)
hsCRP, mg/L	2·7 (147·6)	2·8 (169·6)	2·4 (138·4)	3·0 (151·3)	2·8 (151·9)

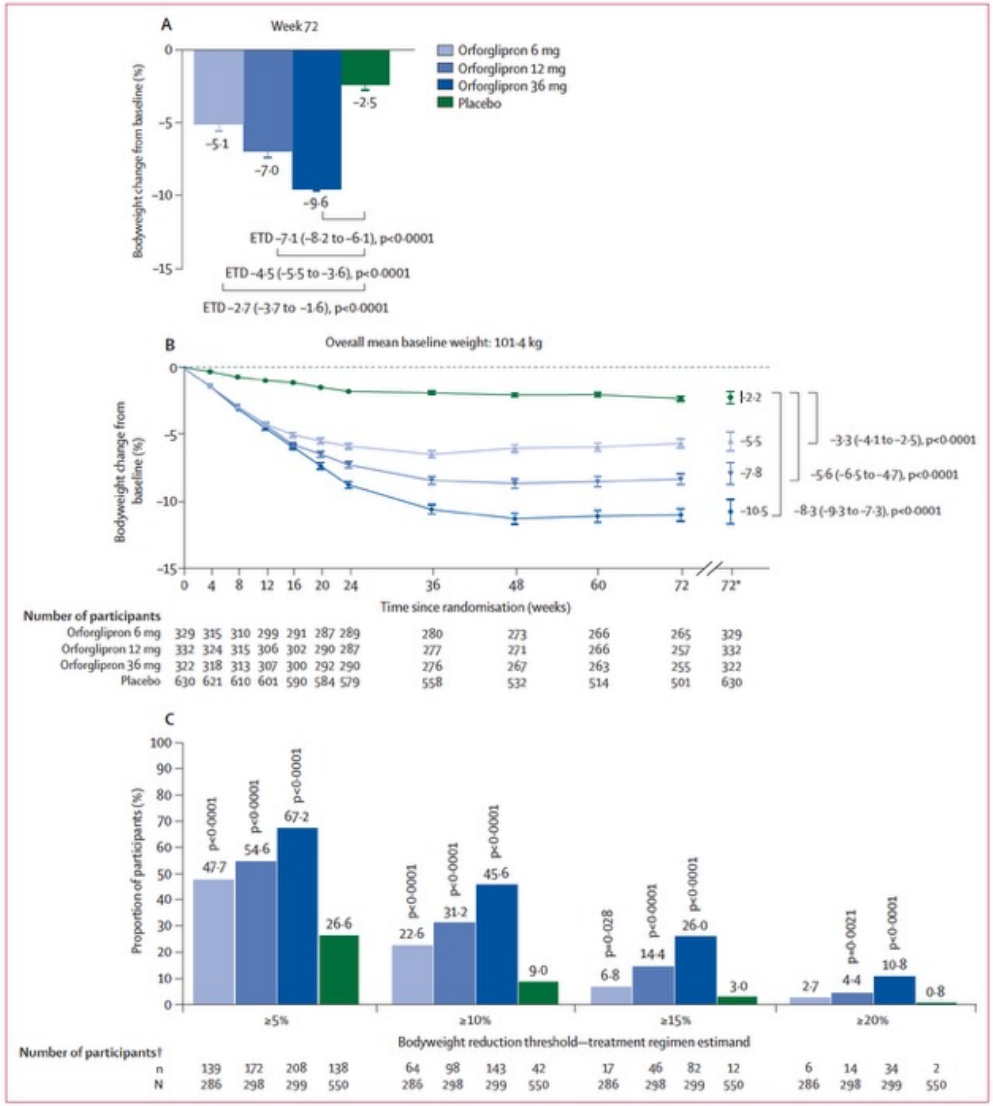
(Table 1 continues on next page)

(Continued from previous page)

	Orforglipron 6 mg (n=329)	Orforglipron 12 mg (n=332)	Orforglipron 36 mg (n=322)	Placebo (n=630)	Total (n=1613)
Antihyperglycaemic drug class					
Biguanides	282 (85·7%)	275 (82·8%)	270 (83·9%)	524 (83·2%)	1351 (83·8%)
Sulfonylureas	40 (12·2%)	51 (15·4%)	50 (15·5%)	83 (13·2%)	224 (13·9%)
SGLT2 inhibitor	105 (31·9%)	97 (29·2%)	109 (33·9%)	206 (32·7%)	517 (32·1%)
Thiazolidinediones	15 (4·6%)	14 (4·2%)	16 (5·0%)	32 (5·1%)	77 (4·8%)
α-glucosidase inhibitors	0	4 (1·2%)	2 (0·6%)	4 (0·6%)	10 (0·6%)
Other‡	0	0	1 (0·3%)	2 (0·3%)	3 (0·2%)
Number of oral antihyperglycaemic drugs					
0	31 (9·4%)	35 (10·5%)	35 (10·9%)	73 (11·6%)	174 (10·8%)
1	176 (53·5%)	172 (51·8%)	146 (45·3%)	311 (49·4%)	805 (49·9%)
2	103 (31·3%)	106 (31·9%)	121 (37·6%)	204 (32·4%)	534 (33·1%)
≥3	19 (5·8%)	19 (5·7%)	20 (6·2%)	42 (6·7%)	100 (6·2%)
Comorbidities§					
Hypertension	252 (76·6%)	233 (70·2%)	246 (76·4%)	470 (74·6%)	1201 (74·5%)
Dyslipidaemia	232 (70·5%)	242 (72·9%)	225 (69·9%)	441 (70·0%)	1140 (70·7%)
Coronary artery disease	19 (5·8%)	21 (6·3%)	27 (8·4%)	49 (7·8%)	116 (7·2%)
Cerebrovascular disease	14 (4·3%)	19 (5·7%)	17 (5·3%)	32 (5·1%)	82 (5·1%)
Obstructive sleep apnoea	49 (14·9%)	45 (13·6%)	34 (10·6%)	86 (13·7%)	214 (13·3%)
Osteoarthritis	71 (21·6%)	57 (17·2%)	78 (24·2%)	112 (17·8%)	318 (19·7%)
Anxiety or depression	45 (13·7%)	50 (15·1%)	42 (13·0%)	86 (13·7%)	223 (13·8%)
MASLD	96 (29·2%)	100 (30·1%)	96 (29·8%)	173 (27·5%)	465 (28·8%)
Asthma or COPD	28 (8·5%)	37 (11·1%)	23 (7·1%)	48 (7·6%)	136 (8·4%)
PCOS¶	3 (2·0%)	1 (0·6%)	4 (2·6%)	6 (2·0%)	14 (1·8%)
Gout or hyperuricaemia	36 (10·9%)	39 (11·7%)	45 (14·0%)	81 (12·9%)	201 (12·5%)
Renal disease	34 (10·3%)	37 (11·1%)	31 (9·6%)	78 (12·4%)	180 (11·2%)
Number of comorbidities in addition to type 2 diabetes					
None	16 (4·9%)	21 (6·3%)	17 (5·3%)	43 (6·8%)	97 (6·0%)
1–2	142 (43·2%)	143 (43·1%)	145 (45·0%)	272 (43·2%)	702 (43·5%)
3–4	124 (37·7%)	129 (38·9%)	111 (34·5%)	224 (35·6%)	588 (36·5%)
≥5	47 (14·3%)	39 (11·7%)	49 (15·2%)	91 (14·4%)	226 (14·0%)

Data are n (%); mean (SD); median (IQR), for duration of obesity and duration of diabetes; or geometric mean (coefficient of variation, %), for lipid parameters, fasting insulin, and hsCRP. bpm=beats per minute. COPD=chronic obstructive pulmonary disease. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin. hsCRP=high-sensitivity C-reactive protein. MASLD=metabolic dysfunction-associated steatotic liver disease. PCOS=polycystic ovarian syndrome. *Race or ethnicity was reported by the participants. †The value of the eGFR was calculated according to the cystatin C-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. ‡Other blood glucose-lowering drugs, excluding insulins. §Comorbidities were assessed through a review of medical history. ¶Percentage is based on the total number of female participants in the respective treatment group: n=150 (orforglipron 6 mg), n=155 (orforglipron 12 mg), n=154 (orforglipron 36 mg), n=298 (placebo), n=757 (total).

Table 1: **Demographic and baseline clinical characteristics of participants**



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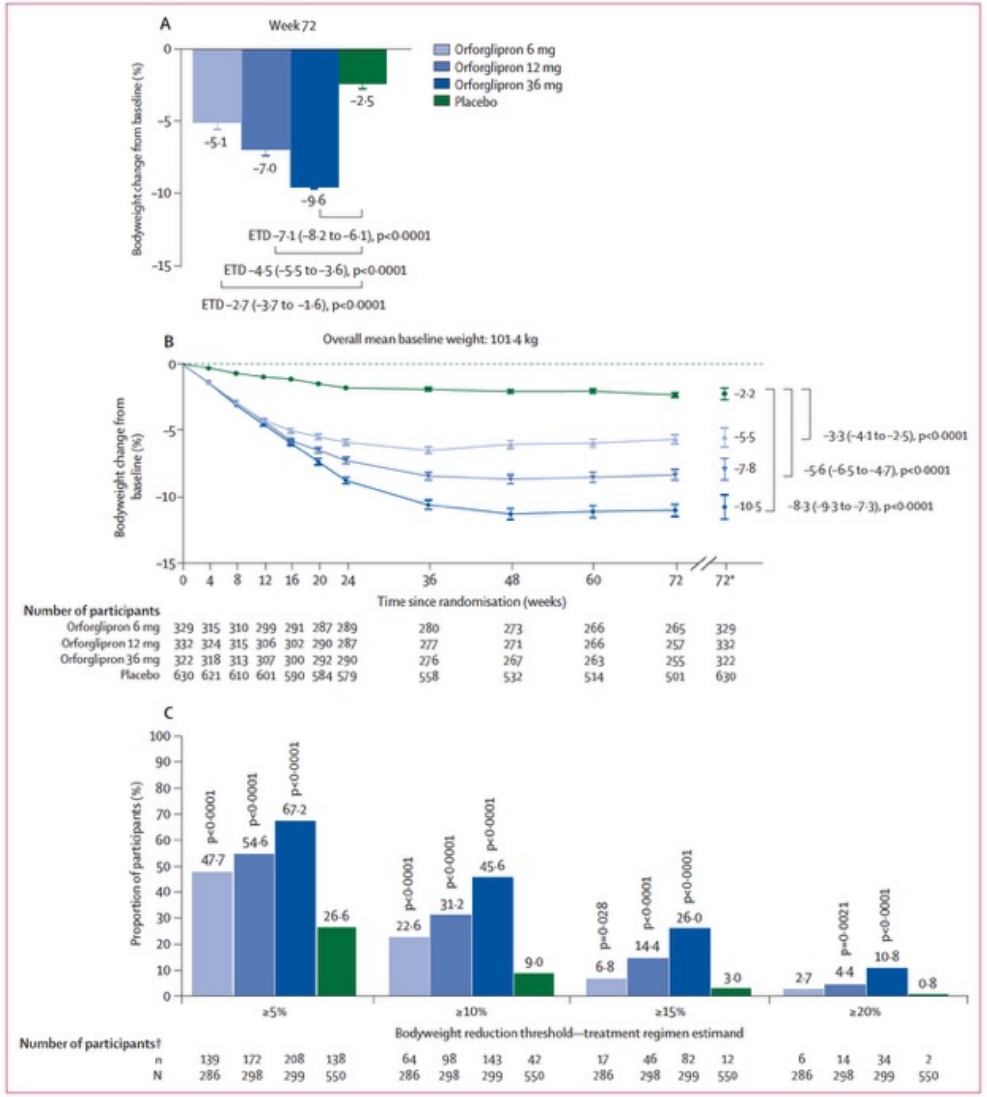

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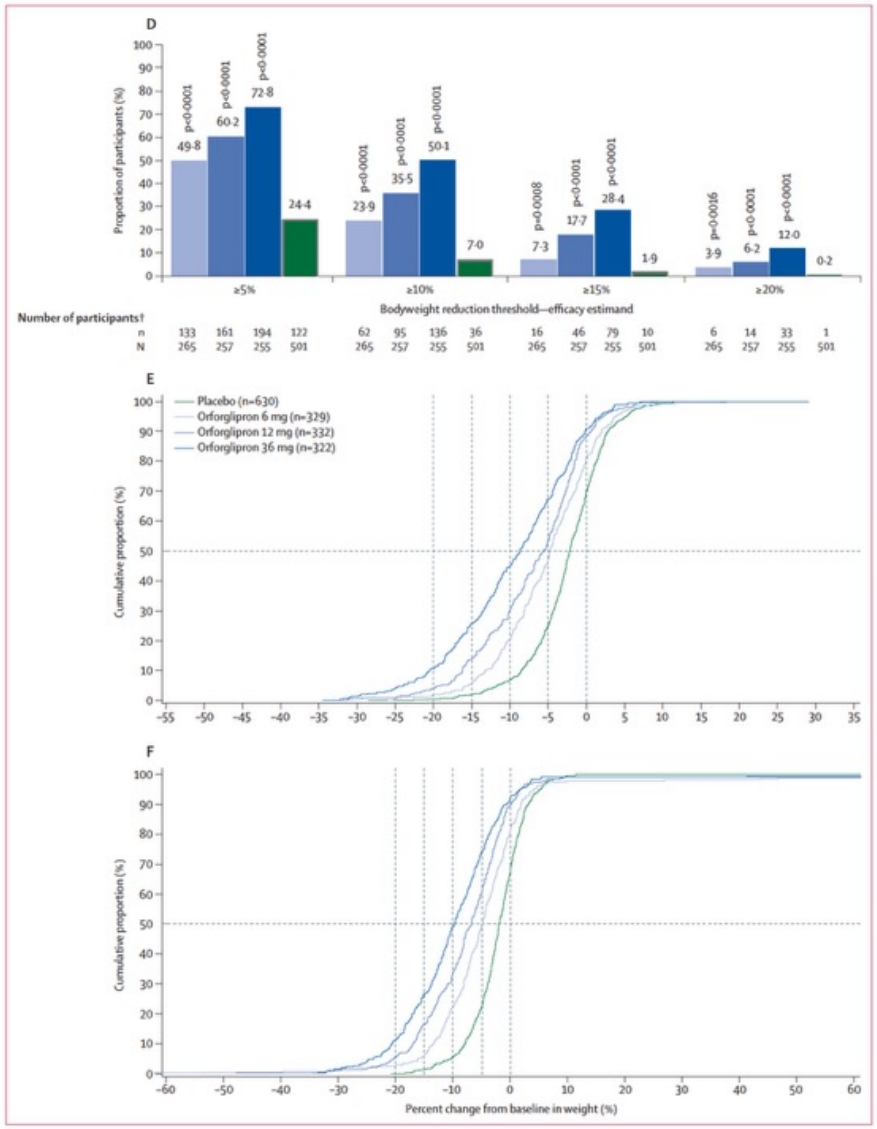


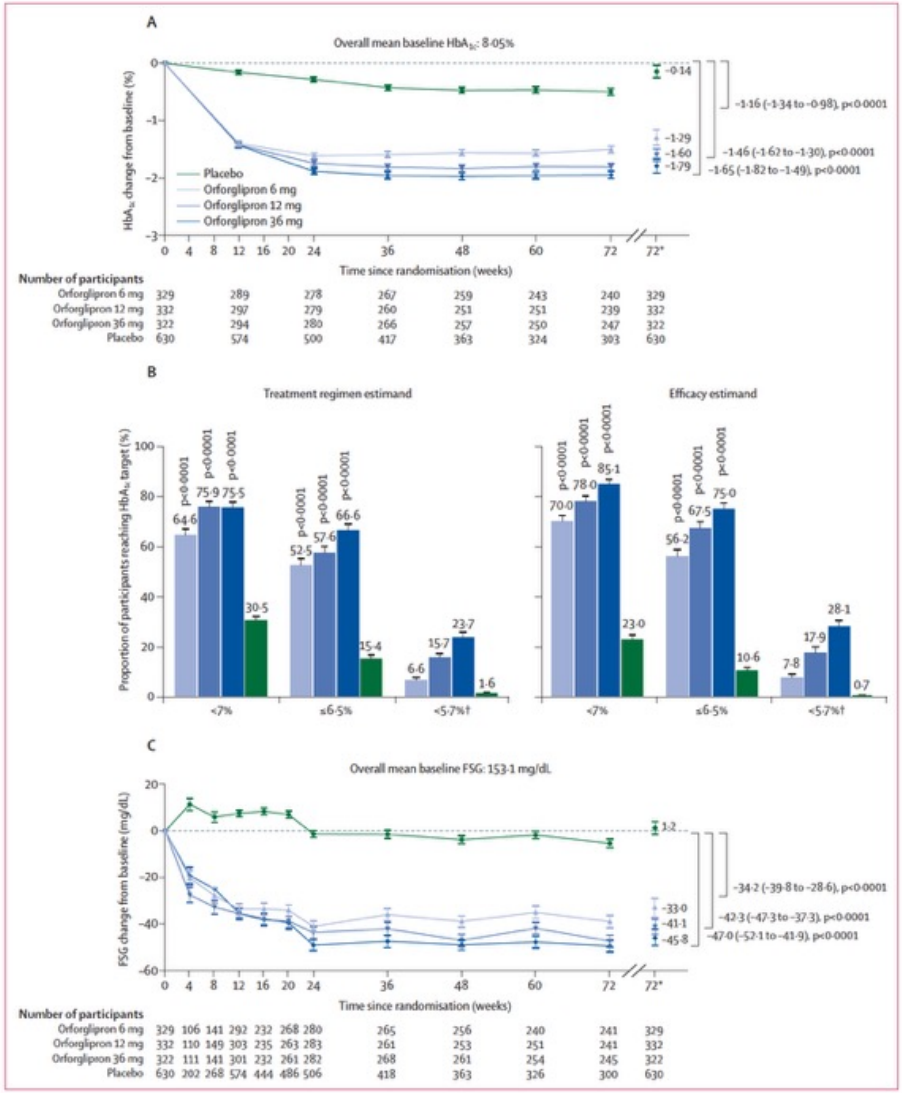
Figure 2: **Bodyweight and bodyweight reduction thresholds**

Data are model-based estimate (MBE) unless otherwise stated. (A) Percent change in bodyweight at week 72 from baseline (treatment regimen estimand). (B) Percent change in bodyweight from baseline to week 72. The curves shown from week 0 to week 72 are based on observed mean with standard errors using the efficacy estimand datapoints set, including all datapoints obtained during the treatment period and up to the earliest date of discontinuation of study treatment or initiation of prohibited weight management treatments. (C, D) Percentage of participants who reached bodyweight reduction thresholds (≥5%, ≥10%, ≥15%, and ≥20%) from logistic regression analysis for the treatment regimen estimand (C) and for the efficacy estimand (D). ≥15% threshold was an additional secondary endpoint for the orforglipron 6 mg dose and not controlled for multiplicity; ≥20% threshold was an exploratory objective and was not controlled for multiplicity. (E) Cumulative distribution of percent change in bodyweight for the treatment regimen estimand; missing data were imputed with primary multiple imputation method. (F) Cumulative distribution of percent change in bodyweight for the efficacy estimand; missing data were imputed using multiple imputation with missing at random assumption. p values refer to comparison with placebo. ETD=estimated treatment difference. *MBE (95% CI) for percent change in bodyweight from baseline to week 72 and ETD (95% CI) between orforglipron groups and placebo based on mixed model for repeated measures analysis (efficacy estimand). †N denotes number of participants with non-missing value at the specified timepoint; n denotes number of participants reaching threshold in observed data.

	Orforglipron 6 mg (n=329)	Orforglipron 12 mg (n=332)	Orforglipron 36 mg (n=322)	Placebo (n=630)
Primary endpoint*				
Percent change in weight, % (95% CI)	−5·1 (−6·0 to −4·2)	−7·0 (−7·8 to −6·2)	−9·6 (−10·5 to −8·7)	−2·5 (−3·0 to −1·9)
Treatment comparison (95% CI); p value	ETD −2·7 (−3·7 to −1·6); p<0·0001	ETD −4·5 (−5·5 to −3·6); p<0·0001	ETD −7·1 (−8·2 to −6·1); p<0·0001	–
Key secondary endpoints*				
Participants with weight reduction ≥5% at week 72, % (SE)†	47·7 (2·9)	54·6 (2·8)	67·2 (2·7)	26·6 (2·0)
Treatment comparison (95% CI); p value	RD 21·1 (14·1 to 28·0); p<0·0001	RD 28·0 (21·4 to 34·7); p<0·0001	RD 40·5 (34·2 to 46·9); p<0·0001	–
Participants with weight reduction ≥10% at week 72, % (SE)†	22·6 (2·5)	31·2 (2·6)	45·6 (2·7)	9·0 (1·4)
Treatment comparison (95% CI); p value	RD 13·6 (8·0 to 19·2); p<0·0001	RD 22·1 (16·5 to 27·7); p<0·0001	RD 36·6 (30·7 to 42·6); p<0·0001	–
Participants with weight reduction ≥15% at week 72, % (SE)†	NA	14·4 (1·9)	26·0 (2·4)	3·0 (0·7)
Treatment comparison (95% CI); p value	..	RD 11·4 (7·4 to 15·3); p<0·0001	RD 22·9 (18·0 to 27·9); p<0·0001	–
Change in waist circumference, cm (95% CI)	NA	NA	−8·3 (−9·2 to −7·5)	−2·8 (−3·4 to −2·3)
Treatment comparison (95% CI); p value	..	..	ETD −5·5 (−6·5 to −4·5); p<0·0001	–
Change in HbA_{1c}, % (95% CI)	−1·22 (−1·36 to −1·08)	−1·50 (−1·62 to −1·38)	−1·66 (−1·77 to −1·55)	−0·47 (−0·58 to −0·36)
Treatment comparison (95% CI); p value	ETD −0·76 (−0·93 to −0·58); p<0·0001	ETD −1·03 (−1·19 to −0·87); p<0·0001	ETD −1·20 (−1·35 to −1·04); p<0·0001	–
Change in HbA_{1c}, mmol/mol (95% CI)	−13·4 (−14·9 to −11·8)	−16·4 (−17·7 to −15·0)	−18·2 (−19·4 to −16·9)	−5·1 (−6·3 to −3·9)
Treatment comparison (95% CI); p value	ETD −8·3 (−10·1 to −6·4); p<0·0001	ETD −11·3 (−13·1 to −9·5); p<0·0001	ETD −13·1 (−14·8 to −11·4); p<0·0001	–
Participants with HbA_{1c} <7%, % (SE)†	64·6 (2·8)	75·9 (2·5)	75·5 (2·5)	30·5 (2·0)
Treatment comparison (95% CI); p value	RD 34·2 (27·4 to 41·0); p<0·0001	RD 45·4 (38·9 to 51·9); p<0·0001	RD 45·1 (38·8 to 51·4); p<0·0001	–
Participants with HbA_{1c} ≤6·5%, % (SE)†	52·5 (3·0)	57·6 (2·8)	66·6 (2·7)	15·4 (1·7)
Treatment comparison (95% CI); p value	RD 37·1 (30·5 to 43·8); p<0·0001	RD 42·2 (35·9 to 48·5); p<0·0001	RD 51·2 (45·0 to 57·5); p<0·0001	–
Change in fasting serum glucose, mg/dL (95% CI)	−30·5 (−35·1 to −26·0)	−38·6 (−42·2 to −35·0)	−42·4 (−46·4 to −38·4)	−9·3 (−13·2 to −5·4)
Treatment comparison (95% CI); p value	ETD −21·2 (−26·8 to −15·6); p<0·0001	ETD −29·2 (−34·2 to −24·3); p<0·0001	ETD −33·1 (−38·3 to −27·8); p<0·0001	–
Change in fasting serum glucose, mmol/L (95% CI)	−1·7 (−1·9 to −1·4)	−2·1 (−2·3 to −1·9)	−2·4 (−2·6 to −2·1)	−0·5 (−0·7 to −0·3)
Treatment comparison (95% CI); p value	ETD −1·2 (−1·5 to −0·9); p<0·0001	ETD −1·6 (−1·9 to −1·4); p<0·0001	ETD −1·8 (−2·1 to −1·5); p<0·0001	–
Additional secondary endpoints (at week 72)				
Change in absolute bodyweight, kg (95% CI)	−5·3 (−6·3 to −4·4)	−7·2 (−8·0 to −6·3)	−9·6 (−10·6 to −8·7)	−2·7 (−3·3 to −2·1)
Treatment comparison (95% CI)	ETD −2·6 (−3·7 to −1·6)	ETD −4·5 (−5·5 to −3·5)	ETD −7·0 (−8·0 to −5·9)	–
Participants with weight reduction ≥15% at week 72, % (SE)†	6·8 (1·5)	NA	NA	3·0 (0·7)
Treatment comparison (95% CI)	RD 3·8 (0·4 to 7·1)	..	..	–
Change in waist circumference, cm (95% CI)	−5·4 (−6·3 to −4·5)	−6·3 (−7·1 to −5·5)	NA	−2·8 (−3·4 to −2·3)
Treatment comparison (95% CI)	ETD −2·6 (−3·6 to −1·5)	ETD −3·5 (−4·5 to −2·5)	..	–
Change in BMI, kg/m² (95% CI)	−1·9 (−2·2 to −1·6)	−2·6 (−2·8 to −2·3)	−3·4 (−3·8 to −3·1)	−1·0 (−1·2 to −0·8)
Treatment comparison (95% CI)	ETD −0·9 (−1·2 to −0·5)	ETD −1·6 (−1·9 to −1·2)	ETD −2·5 (−2·8 to −2·1)	–
Participants with HbA_{1c} <5·7%, % (SE)†	6·6 (1·4)	15·7 (2·0)	23·7 (2·4)	1·6 (0·6)
Treatment comparison (95% CI)	RD 5·0 (2·1 to 7·9)	RD 14·1 (10·0 to 18·2)	RD 22·0 (17·3 to 26·8)	–
Percent change in fasting insulin, % (95% CI)	−5·1 (−10·4 to 0·5)	−11·9 (−17·4 to −6·0)	−19·8 (−24·7 to −14·7)	−4·2 (−8·8 to 0·7)
Treatment comparison (95% CI)	ETD −1·0 (−8·1 to 6·6)	ETD −8·0 (−15·2 to −0·3)	ETD −16·4 (−22·5 to −9·7)	–
Exploratory objective (at week 72)				
Percent change in hsCRP, % (95% CI)	−32·4 (−39·8 to −24·2)	−41·8 (−47·0 to −36·1)	−47·5 (−52·7 to −41·7)	−10·0 (−16·4 to −3·1)
Treatment comparison (95% CI)	ETD −24·9 (−34·4 to −14·1)	ETD −35·3 (−42·3 to −27·5)	ETD −41·6 (−48·6 to −33·7)	–

Data are model-based estimate and 95% CI assessed with the use of ANCOVA according to the treatment regimen estimand. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. All changes are at week 72 from baseline. Lipid parameters, fasting insulin, and hsCRP were analysed using log-transformation. ETD=estimated treatment difference. HbA_{1c}=glycated haemoglobin. hsCRP=high-sensitivity C-reactive protein. NA=not applicable (the corresponding endpoint does not belong to the category of endpoints [primary, key secondary, or additional secondary] presented in that section of the table). RD=risk difference. *The primary and key secondary endpoints were tested under type I error control procedure using a two-sided nominal significance level of 0·05. †Data presented as model-based estimate (SE) from logistic regression according to the treatment regimen estimand. The percentage was calculated by combining the percentages of participants who met the target in imputed datasets with the use of Rubin's rules.

Table 2: **Primary and secondary endpoints by treatment group—treatment regimen datapoint set**



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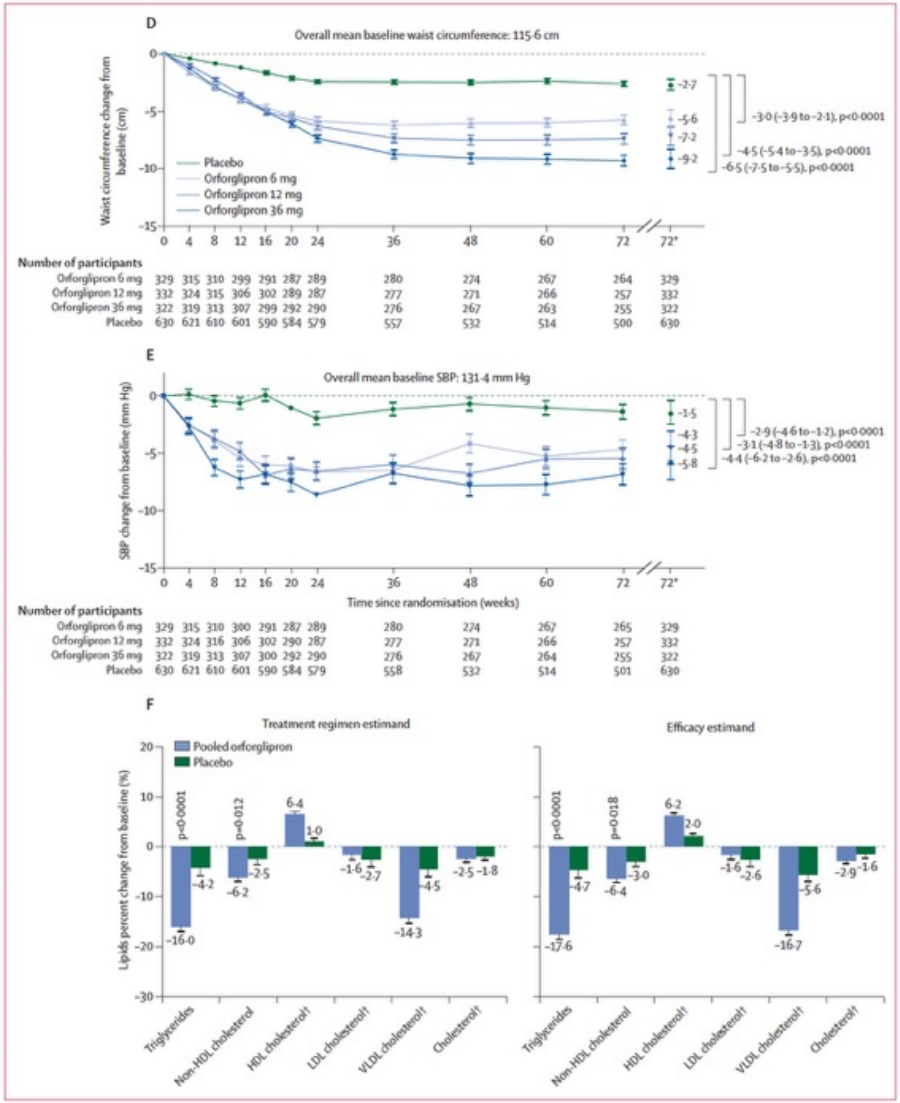


Figure 3: **Effects of orforglipron on HbA_{1c}, FSG, waist circumference, SBP, and lipid levels**

Data are model-based estimate (MBE) unless otherwise stated. Error bars indicate 95% CI. (A, C–E) The curves shown from week 0 to week 72 are based on observed mean with standard errors using the efficacy estimand datapoints set, including all datapoints obtained during the treatment period and up to the earliest date of discontinuation of study treatment or initiation of prohibited weight management treatments (or glycaemic rescue therapy or prohibited glycaemic therapy for glycaemic endpoints only) for change in HbA_{1c} (A), FSG (C), waist circumference (D), and SBP (E). (B) Proportion of participants reaching HbA_{1c} targets (<7·0%, ≤6·5%, and <5·7%) from logistic regression with multiple imputation analysis for the treatment regimen estimand (left) and the efficacy estimand (right). (F) Percent change in fasting lipid levels for pooled orforglipron doses (contains all orforglipron groups: 6 mg, 12 mg, and 36 mg) and placebo from baseline to week 72 from ANCOVA for the treatment regimen estimand and mixed model for repeated measures (MMRM) for the efficacy estimand; results for the orforglipron by-dose analysis are available in the appendix (pp 48–52). FSG=fasting serum glucose. HbA_{1c}=glycated haemoglobin. SBP=systolic blood pressure. *MBE (95% CI) for change in HbA_{1c} (A), FSG (C), waist circumference (D), and SBP (E) from baseline to week 72 and estimated treatment difference (95% CI) between orforglipron groups and placebo based on MMRM analysis (efficacy estimand). †Not controlled for multiplicity.

	Pooled orforglipron (n=983)	Placebo (n=630)
Key secondary endpoints*		
Change in SBP, mm Hg (95% CI)	−4·2 (−5·1 to −3·3)	−1·6 (−2·7 to −0·4)
Treatment comparison (95% CI); p value	ETD −2·6 (−4·0 to −1·3); p=0·0002	..
Percent change in non-HDL cholesterol, % (95% CI)	−6·2 (−8·0 to −4·4)	−2·5 (−4·9 to −0·2)
Treatment comparison (95% CI); p value	ETD −3·8 (−6·6 to −0·8); p=0·0124	..
Percent change in triglycerides, % (95% CI)	−16·0 (−18·2 to −13·7)	−4·2 (−7·6 to −0·8)
Treatment comparison (95% CI); p value	ETD −12·2 (−15·9 to −8·4); p<0·0001	..
Additional secondary endpoints (at week 72)		
Change in DBP, mm Hg (95% CI)	−1·5 (−2·1 to −1·0)	−1·3 (−2·0 to −0·5)
Treatment comparison (95% CI)	ETD −0·3 (−1·2 to 0·6)	..
Percent change in total cholesterol, % (95% CI)	−2·5 (−3·9 to −1·2)	−1·8 (−3·7 to 0·1)
Treatment comparison (95% CI)	ETD −0·7 (−3·0 to 1·6)	..
Percent change in LDL cholesterol, % (95% CI)	−1·6 (−3·8 to 0·6)	−2·7 (−5·6 to 0·4)
Treatment comparison (95% CI)	ETD 1·1 (−2·6 to 4·8)	..
Percent change in HDL cholesterol, % (95% CI)	6·4 (5·2 to 7·7)	1·0 (−0·6 to 2·5)
Treatment comparison (95% CI)	ETD 5·4 (3·4 to 7·4)	..

Pooled refers to pooled orforglipron 6 mg, 12 mg, and 36 mg groups. Model estimates for pooled orforglipron are estimated via a linear contrast that averages estimates from individual treatment groups. All changes are at week 72 from baseline. DBP=diastolic blood pressure. ETD=estimated treatment difference. SBP=systolic blood pressure.
*The primary and key secondary endpoints were tested under type I error control procedure using a two-sided nominal significance level of 0·05.

Table 3: **Secondary endpoints by pooled treatment group—treatment regimen datapoint set**

	Orforglipron 6 mg (n=328)	Orforglipron 12 mg (n=331)	Orforglipron 36 mg (n=321)	Placebo (n=628)	Overall (n=1608)	Risk difference (95% CI)		
						Orforglipron 6 mg *vs* placebo	Orforglipron 12 mg *vs* placebo	Orforglipron 36 mg *vs* placebo
Participants with ≥1 TEAE	270 (82·3%)	290 (87·6%)	284 (88·5%)	545 (86·8%)	1389 (86·4%)	−4·5 (−9·4 to 0·4)	0·8 (−3·6 to 5·3)	1·7 (−2·7 to 6·1)
Serious adverse events	24 (7·3%)	34 (10·3%)	35 (10·9%)	55 (8·8%)	148 (9·2%)	−1·4 (−5·0 to 2·1)	1·5 (−2·4 to 5·5)	2·2 (−1·9 to 6·2)
Deaths*	0	4 (1·2%)	2 (0·6%)	4 (0·6%)	10 (0·6%)	−0·6 (−1·3 to −0·01)	0·6 (−0·8 to 1·9)	−0·01 (−1·1 to 1·1)
Adverse events leading to discontinuation of study drug	20 (6·1%)	35 (10·6%)	34 (10·6%)	29 (4·6%)	118 (7·3%)	1·5 (−1·6 to 4·6)	6·0 (2·3 to 9·7)	6·0 (2·2 to 9·7)
Nausea	2 (0·6%)	8 (2·4%)	6 (1·9%)	0	16 (1·0%)	0·6 (−0·2 to 1·5)	2·4 (0·8 to 4·1)	1·9 (0·4 to 3·4)
Vomiting	5 (1·5%)	5 (1·5%)	4 (1·2%)	0	14 (0·9%)	1·5 (0·2 to 2·9)	1·5 (0·2 to 2·8)	1·3 (0·0 to 2·5)
Diarrhoea	2 (0·6%)	5 (1·5%)	3 (0·9%)	1 (0·2%)	11 (0·7%)	0·5 (−0·5 to 1·4)	1·4 (0·0 to 2·7)	0·8 (−0·3 to 1·9)
Abdominal pain	0	1 (0·3%)	1 (0·3%)	1 (0·2%)	3 (0·2%)	−0·2 (−0·5 to 0·2)	0·1 (−0·5 to 0·8)	0·2 (−0·5 to 0·8)
TEAEs occurring in ≥5% of participants in any treatment group (preferred term)								
Nausea	66 (20·1%)	103 (31·1%)	117 (36·4%)	53 (8·4%)	339 (21·1%)	11·7 (6·8 to 16·5)	22·7 (17·2 to 28·1)	28·0 (22·3 to 33·7)
Diarrhoea	70 (21·3%)	82 (24·8%)	88 (27·4%)	94 (15·0%)	334 (20·8%)	6·4 (1·1 to 11·6)	9·8 (4·4 to 15·2)	12·5 (6·8 to 18·1)
Constipation	58 (17·7%)	70 (21·1%)	72 (22·4%)	49 (7·8%)	249 (15·5%)	9·9 (5·3 to 14·5)	13·4 (8·5 to 18·2)	14·6 (9·6 to 19·7)
Vomiting	42 (12·8%)	67 (20·2%)	74 (23·1%)	24 (3·8%)	207 (12·9%)	9·0 (5·1 to 12·9)	16·4 (11·8 to 21·0)	19·2 (14·4 to 24·1)
Dyspepsia	30 (9·1%)	51 (15·4%)	35 (10·9%)	22 (3·5%)	138 (8·6%)	5·6 (2·2 to 9·1)	11·9 (7·8 to 16·1)	7·4 (3·7 to 11·1)
Decreased appetite	27 (8·2%)	30 (9·1%)	49 (15·3%)	18 (2·9%)	124 (7·7%)	5·4 (2·1 to 8·6)	6·2 (2·8 to 9·6)	12·4 (8·3 to 16·5)
Eructation	21 (6·4%)	38 (11·5%)	28 (8·7%)	4 (0·6%)	91 (5·7%)	5·8 (3·0 to 8·5)	10·8 (7·4 to 14·3)	8·1 (4·9 to 11·2)
Headache	17 (5·2%)	19 (5·7%)	22 (6·9%)	33 (5·3%)	91 (5·7%)	−0·1 (−3·0 to 2·9)	0·5 (−2·6 to 3·5)	1·6 (−1·7 to 4·9)
Abdominal pain	19 (5·8%)	20 (6·0%)	18 (5·6%)	17 (2·7%)	74 (4·6%)	3·1 (0·3 to 5·9)	3·3 (0·5 to 6·2)	2·9 (0·1 to 5·7)
Dizziness	19 (5·8%)	11 (3·3%)	22 (6·9%)	18 (2·9%)	70 (4·4%)	2·9 (0·1 to 5·8%)	0·5 (−1·9 to 2·8)	4·0 (0·9 to 7·0)
Adverse events of special interest								
Treatment-emergent hepatic events†	0	5 (1·5%)	2 (0·6%)	2 (0·3%)	9 (0·6%)	..	..	..
Malignancies	4 (1·2%)	3 (0·9%)	8 (2·5%)	11 (1·8%)	26 (1·6%)	−0·5 (−2·1 to 1·0)	−0·9 (−2·3 to 0·6)	0·7 (−1·3 to 2·7)
Diabetic retinopathy	23 (7·0%)	23 (6·9%)	22 (6·9%)	43 (6·8%)	111 (6·9%)	0·2 (−3·2 to 3·6)	0·1 (−3·3 to 3·5)	0·01 (−3·4 to 3·4)
Pancreatitis (adjudication-confirmed)	0	1 (0·3%)	0	2 (0·3%)	3 (0·2%)	..	..	..
MACE (adjudication-confirmed)	1 (0·3%)	8 (2·4%)	7 (2·2%)	9 (1·4%)	25 (1·6%)	..	..	..
Treatment-emergent cardiac events‡	4 (1·2%)	3 (0·9%)	5 (1·6%)	6 (1·0%)	18 (1·1%)	..	..	..
Gastrointestinal events†	12 (3·7%)	15 (4·5%)	14 (4·4%)	8 (1·3%)	49 (3·0%)	2·4 (0·2 to 4·6)	3·3 (0·9 to 5·7)	3·1 (0·7 to 5·5)
Gallbladder disease†	1 (0·3%)	3 (0·9%)	3 (0·9%)	4 (0·6%)	11 (0·7%)	..	..	..
Renal events†	0	4 (1·2%)	0	1 (0·2%)‖	5 (0·3%)	..	..	..
MDD or suicidal ideation†	1 (0·3%)	1 (0·3%)	0	2 (0·3%)	4 (0·2%)	..	..	..
Hypersensitivity†	1 (0·3%)	0	0	0	1 (0·1%)	..	..	..
Dysaesthesia§	5 (1·5%)	3 (0·9%)	8 (2·5%)	8 (1·3%)	24 (1·5%)	0·3 (−1·3 to 1·8);	−0·4 (−1·7 to 1·0);	1·2 (−0·7 to 3·1);
Other TEAEs of interest								
Hypoglycaemia¶	5 (1·5%)	7 (2·1%)	8 (2·5%)	2 (0·3%)	22 (1·4%)	0·9 (0·1 to 9·9)	1·2 (0·1 to 12·5)	1·2 (0·1 to 12·1)
Severe hypoglycaemia‖	1 (0·3%)	0	0	0	1 (<0·1%)	..	..	..
Initiation of rescue therapy for severe persistent hyperglycaemia	34 (10·4%)	23 (6·9%)	15 (4·7%)	239 (38·1%)	311 (19·3%)	..	..	..
Cholelithiasis	4 (1·2%)	7 (2·1%)	2 (0·6%)	2 (0·3%)	15 (0·9%)	0·9 (−0·4 to 2·2)	1·8 (0·2 to 3·4)	0·3 (−0·7 to 1·3)
Acute cholecystitis	1 (0·3%)	1 (0·3%)	2 (0·6%)	2 (0·3%)	6 (0·4%)	−0·01 (−0·8 to 0·7)	−0·02 (−0·8 to 0·7)	0·3 (−0·7 to 1·3)
Chronic cholecystitis	0	0	1 (0·3%)	0	1 (0·1%)	0	0	0·3 (−0·3 to 0·9)

Data are shown as number of participants (%) unless otherwise stated. For the blank cells, data were unavailable. MACE=major adverse cardiovascular event. MDD=major depressive disorder. TEAE=treatment-emergent adverse event. *Deaths are also included as serious adverse events and discontinuations due to adverse events. †Events were classified as severe or serious adverse events. ‡Events that were classified as severe or serious arrhythmias and cardiac conduction disorders. §Includes MedDRA search terms of burning sensation, hyperaesthesia, dysaesthesia, sensitive skin, pain of skin, and paraesthesia. ¶Hypoglycaemia was defined as a blood glucose of <54 mg/dL (3·0 mmol/L). Events occurring within a 1-h period were considered as one event. The event with the highest severity was selected for analysis. ‖Severe hypoglycaemia was defined as a hypoglycaemic event characterised by altered mental status and/or altered physical status that the participant was unable to resolve without assistance. Events occurring within a 1-h period were considered as one event. The event with the highest severity was selected for analysis.

***Table 4*: Adverse events in the safety population**

Research in context

Evidence before this study

Strong and consistent evidence demonstrates the benefit of managing obesity in people with type 2 diabetes. Weight reduction improves glycaemia, functional status, and quality of life, and reduces the need for glucose-lowering medications in people with obesity and type 2 diabetes. Additionally, greater weight reduction can promote sustained diabetes remission. On June 18, 2025, we searched PubMed using the search terms "glucagon-like peptide-1 receptor agonist" (GLP-1 receptor agonist), AND "obesity", AND "overweight", AND "type 2 diabetes" for any published articles, with no date or language restrictions.

To date, two GLP-1 receptor monoagonists, liraglutide (3 mg once daily) and semaglutide (2·4 mg once weekly), and tirzepatide, a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist, all peptides in injectable formulations, have been approved for weight management. The oral formulation of semaglutide (7 mg and 14 mg once per day) is approved for type 2 diabetes treatment; higher doses are being investigated to treat obesity but are not yet approved.

Orforglipron, a once-daily, oral, small-molecule (non-peptide) GLP-1 receptor agonist was investigated for obesity treatment as an adjunct to lifestyle modification in two global, placebo-controlled phase 3 trials in people with obesity without diabetes (ATTAIN-1) and with type 2 diabetes (ATTAIN-2). Results of the ATTAIN-2 trial are reported herein.

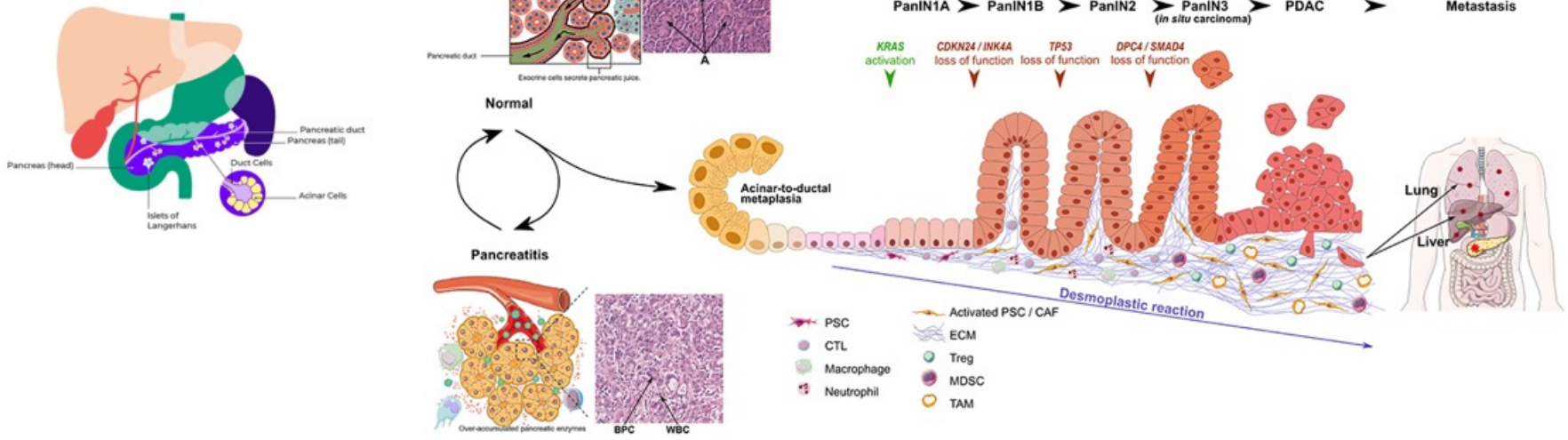
Added value of this study

ATTAIN-2 is the first completed long-term (72-week) trial with a once-daily, oral, small-molecule GLP-1 receptor agonist, as an adjunct to lifestyle modification, in adults with a BMI of 27 kg/m² or higher and type 2 diabetes with the primary objective focusing on bodyweight changes. In this trial, orforglipron demonstrated clinically meaningful reductions in bodyweight along with improvements in glycaemic control and cardiometabolic risk factors. The mean bodyweight reduction at week 72 was up to 9·6% at the highest orforglipron dose, and a substantial proportion of participants reached weight loss of 10% or greater or 15% or greater. The results exceed what is typically seen in this population with currently available oral medications for obesity management. Additionally, glycated haemoglobin (HbA_{1c}) reduction of up to 1·66%, and a substantial proportion of participants reaching HbA_{1c} levels less than 7% (75·5%) and less than or equal to 6·5% (66·6%) with orforglipron 36 mg, highlight the dual benefit of orforglipron for both weight reduction and glycaemic improvement, addressing the challenge of managing both obesity and diabetes simultaneously. Observed reductions in waist circumference, systolic blood pressure, non-HDL cholesterol, and triglycerides suggest that orforglipron could offer broad cardiometabolic benefits, which is particularly important given the elevated cardiovascular risk in this population. Overall, the findings indicate that orforglipron could address the unmet need for oral therapy by achieving outcomes similar to those of injectable GLP-1 receptor agonists, potentially shifting treatment paradigms.

Implications of all the available evidence

In this phase 3 trial in adults with obesity and type 2 diabetes, orforglipron demonstrated clinically meaningful bodyweight reduction. Bodyweight reductions and improvements in glucose control and other cardiometabolic risk markers observed in this study were consistent with previous orforglipron trials in people with obesity without diabetes (ATTAIN-1) and in people with early type 2 diabetes with a BMI of 23 kg/m² or higher (ACHIEVE-1). As a non-peptide oral, orforglipron is simple to administer, with no restrictions on food and water intake or required refrigeration, potentially offering a more convenient option and broader global access to incretin therapy.

Pancreatic ductal adenocarcinoma (PDAC) is the most common and aggressive type of pancreatic cancer, starting in the cells lining the pancreas's ducts that carry digestive enzymes, and is known for its poor prognosis due to late diagnosis. It's characterized by abnormal cell growth, often in the head of the pancreas, with symptoms like abdominal/back pain, jaundice, and weight loss, though it's often silent early on. Risk factors include smoking, diabetes, chronic pancreatitis, and family history, with a high fatality rate making it a major focus for research.



Preoperative mFOLFIRINOX versus PAXG for stage I–III resectable and borderline resectable pancreatic ductal adenocarcinoma (PACT-21 CASSANDRA): results of the first randomisation analysis of a randomised, open-label, 2 × 2 factorial phase 3 trial

Summary

Background Perioperative chemotherapy is a standard option for treatment of patients with resectable and borderline resectable pancreatic ductal adenocarcinoma (PDAC). This study aimed to assess the superiority of PAXG (cisplatin, nab-paclitaxel, capecitabine, and gemcitabine) over mFOLFIRINOX (modified fluorouracil, leucovorin, irinotecan, and oxaliplatin) in this population.

Methods CASSANDRA is a randomised, open-label, 2×2 factorial phase 3 trial, involving 17 Italian academic hospitals. Eligible patients were aged 18–75 years with pathologically confirmed resectable or borderline resectable PDAC. Randomisation was performed by a central web-based system using R-code lists with a computerised algorithm. The design adopted a 1:1 randomisation, with a block stratification by centre and carbohydrate antigen 19-9. Participants were first randomly assigned PAXG (total daily capecitabine dose of 1250 mg/m² in a 625 mg/m² twice a day dosage and intravenous cisplatin 30 mg/m², nab-paclitaxel 150 mg/m², and gemcitabine 800 mg/m² every 14 days) or mFOLFIRINOX (intravenous fluorouracil 2400 mg/m², leucovorin 400 mg/m², irinotecan 150 mg/m², and oxaliplatin 85 mg/m² every 14 days) for 4 months, followed by a second randomisation to 2 months of additional chemotherapy either before or after surgery. The primary endpoint was event-free survival (EFS) in the intention-to-treat population and the safety population included all patients who received at least one cycle of the assigned therapy. The results of the first randomisation are reported here. The trial, registered on ClinicalTrials.gov (NCT04793932) and EudraCT (2020-003080-26 and 2024-519031-42-00), completed accrual and reached the necessary events for first randomisation primary analysis but follow-up of overall survival is ongoing.

Findings Between Nov 3, 2020, and April 24, 2024, 132 eligible patients were assigned to PAXG and 128 to mFOLFIRINOX. In the PAXG group, the median age was 65 years (IQR 60–70), 68 (52%) of 132 patients were female, and 64 (48%) were male. In the mFOLFIRNOX group, the median age was 63 years (IQR 57–69), 62 (48%) of 128 patients were female, and 66 (52%) were male. All 260 patients received at least one assigned chemotherapy administration. PAXG prolonged the median EFS compared with mFOLFIRINOX (16·0 months [95% CI 12·4–19·8] *vs* 10·2 months [8·6–13·5]; hazard ratio 0·63 [0·47–0·84]; p=0·0018). At least one grade 3 or worse adverse event was observed in 87 (66%) of 132 patients in the PAXG group and in 78 (61%) of 128 patients in the mFOLFIRINOX group, including one fatal event.

Interpretation PAXG significantly improved EFS compared with mFOLFIRINOX in resectable or borderline resectable PDAC. Preopertive PAXG could be considered a standard option for resectable or borderline resectable PDAC. Accordingly, preoperative PAXG should be considered as the standard comparator group for future trials in this setting.

Funding MyEverest and Codice Viola.

Perioperative chemotherapy is a comprehensive approach that **includes both neoadjuvant and adjuvant phases**, meaning chemotherapy is given *before* surgery (neoadjuvant) to shrink the tumor, *and after* surgery (adjuvant) to eliminate remaining cancer cells, aiming to improve outcomes by tackling the cancer systemically around the surgical window. While neoadjuvant therapy shrinks the tumor for easier surgery and adjuvant therapy kills leftover cells, perioperative treatment combines these to maximize effectiveness, especially in cancers like gastric or esophageal cancer.

EFS = event-free survival

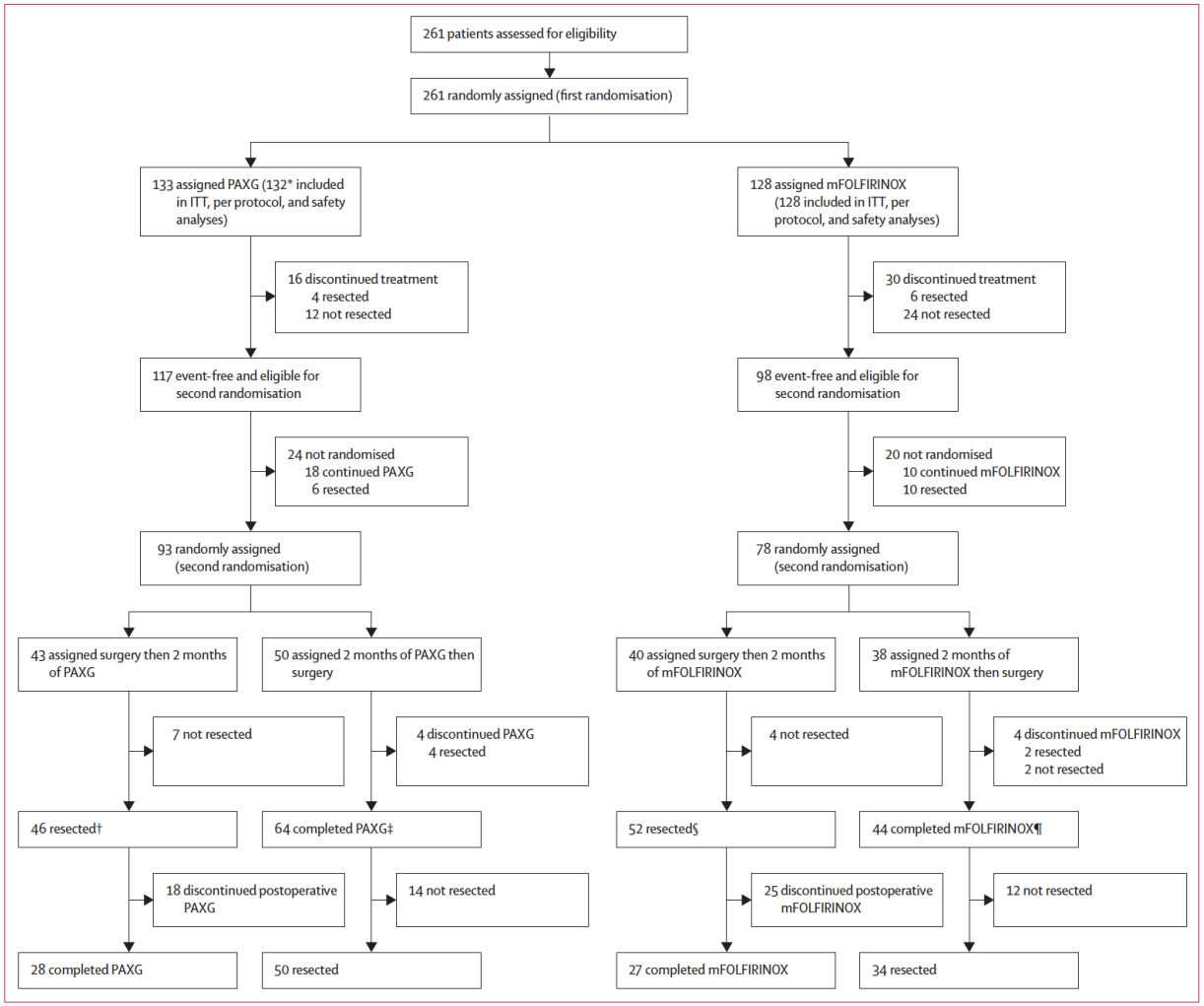


Figure 1: Trial profile
ITT=intention-to-treat. *One patient in the PAXG group had a pathological diagnosis of ampullary carcinoma at final histology after surgery, thus was excluded from the analyses. †Includes four resected before completion of first stage and six resected at second randomisation. ‡Includes 18 patients who did not undergo second randomisation and completed 6 months of PAXG. §Includes six resected before completion of first stage and ten resected at second randomisation. ¶Includes ten patients that did not undergo second randomisation and completed 6 months of mFOLFIRINOX.

	PAXG (n=132)	mFOLFIRINOX (n=128)
Age, years	65 (60–70)	63 (57–69)
<65	66 (50%)	76 (59%)
≥65	66 (50%)	52 (41%)
Sex		
Male	64 (48%)	66 (52%)
Female	68 (52%)	62 (48%)
Race		
White	132 (100%)	128 (100%)
Karnofsky performance status		
≤80	9 (7%)	11 (9%)
90-100	123 (93%)	117 (91%)
Anatomical classification		
Resectable	63 (48%)	63 (49%)
Borderline resectable*	69 (52%)	65 (51%)
CA19-9		
Positive	100 (76%)	85 (66%)
Negative	32 (24%)	43 (34%)
Median (95% CI)†	261 (85–940)	226 (116–940)
≤5 × ULN	71 (54%)	79 (62%)
>5 × ULN	61 (46%)	49 (38%)
Clinical tumour staging		
I	71 (54%)	57 (45%)
II	50 (38%)	58 (45%)
III	11 (8%)	13 (10%)
Tumour location		
Head	93 (70%)	96 (75%)
Uncinate process	11 (8%)	9 (7%)
Body	17 (13%)	16 (13%)
Tail	10 (8%)	6 (5%)
Diffuse	1 (1%)	1 (1%)
Genetic variants‡		
Not available	36 (27%)	36 (28%)
Pathogenic	16/96 (17%)	12/92 (13%)
BRCA1 or *BRCA2* gPV	11/96 (11%)	4/92 (4%)
Other gPVs§	5/96 (5%)	8/92 (9%)
None	80/96 (83%)	80/92 (87%)

Data are as median (range), n (%), or n/N (%), unless otherwise stated. CA19-9=carbohydrate antigen 19-9. ULN=upper limit of normal. gPV=germline pathogenic variant. *Patients were included in the borderline resectable population based on both surgical and biological criteria (CA19-9 of 500 IU/mL or greater). †Median values and 95% CIs are calculated for the group of patients with positive CA19-9 values. ‡Genetic testing results refer to germline variants only. §Includes germline pathogenic variants in *ATM*, *MLH1*, *MSH3*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, and *SDHB*.

Table 1: **Baseline characteristics in the intention-to-treat population by treatment regimen**

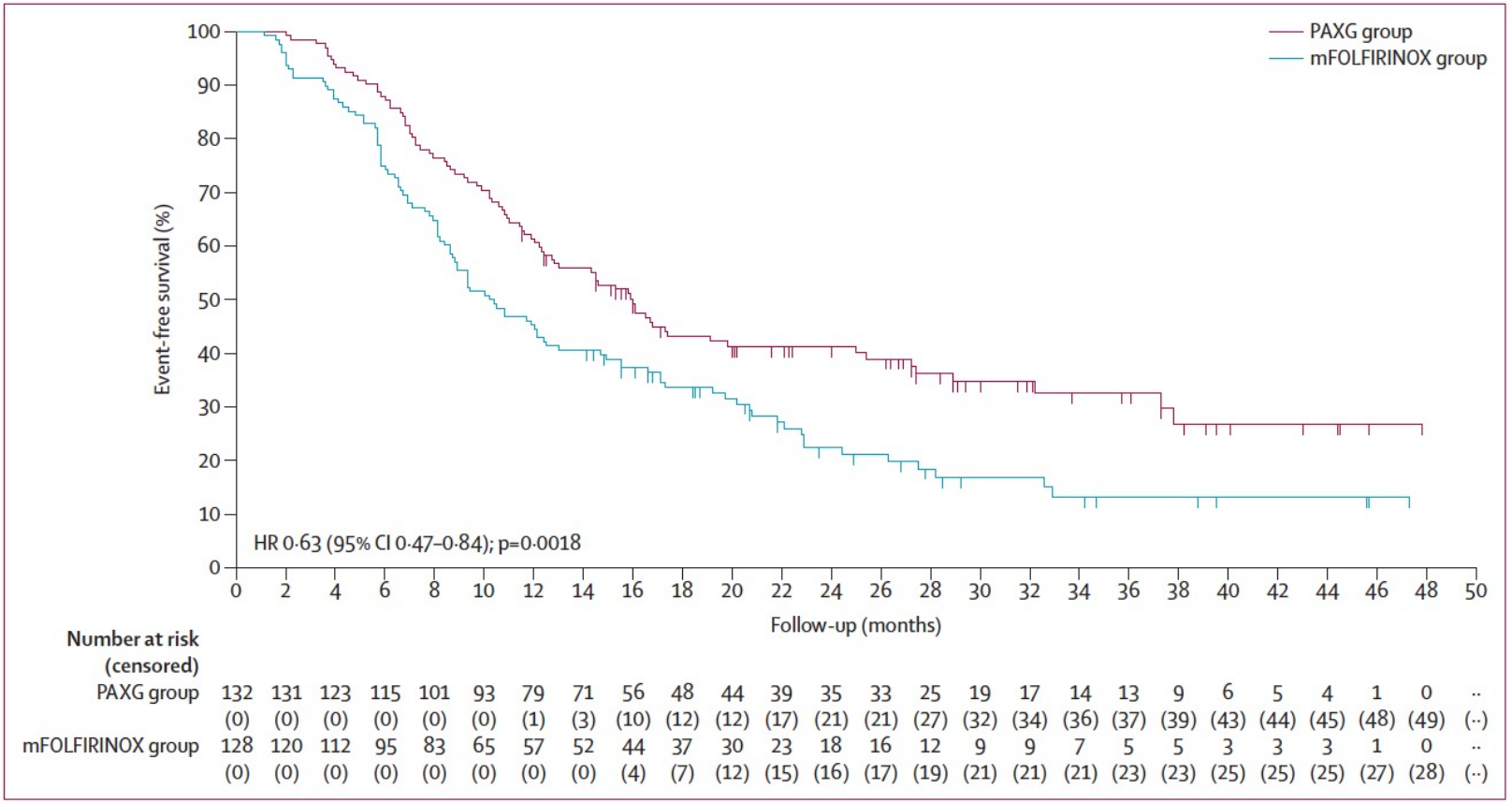


Figure 2: **Kaplan–Meier plot of event-free survival in the intention-to-treat population**
Median event-free survival in PAXG group was 16·0 months (95% CI 12·4–19·8) and in mFOLFIRINOX group was 10·2 months (8·6–13·5). HR=hazard ratio.

	PAXG (n=132)	mFOLFIRINOX (n=128)	Relative response increase (95% CI)	p value
RECIST best response	..	..	..	..
Partial response	61 (46%)	50 (39%)	..	..
Stable disease	69 (52%)	67 (52%)	..	..
Progression of disease	2 (2%)	11 (9%)	..	..
Objective response rate	..	..	1·18 (0·89–1·57)	0·25
No	71 (54%)	78 (61%)	..	..
Yes	61 (46%)	50 (39%)	..	..
Disease control rate	..	..	1·08 (1·02–1·14)	0·0088
No	2 (2%)	11 (9%)	..	..
Yes	130 (98%)	117 (91%)	..	..
CA19-9 response	..	..	1·38 (1·15–1·65)	<0·0001
Not applicable	32 (24%)	43 (34%)	..	..
Missing	3 (2%)	0	..	..
No	12/97 (12%)	31/85 (36%)	..	..
Yes	85/97 (88%)	54/85 (64%)	..	..
Pathological stage	..	..	..	..
IA*	31 (23%)	17 (13%)	..	..
IB	15 (11%)	12 (9%)	..	..
IIA	0	0	..	..
IIB	39 (30%)	32 (25%)	..	..
III	13 (10%)	22 (17%)	..	..
IV	1 (1%)	5 (4%)	..	..
Not resected	33 (25%)	40 (31%)	..	..
Pathological stage <II	..	..	1·54 (1·04–1·29)	0·030
No	86 (65%)	99 (77%)	..	..
Yes	46 (35%)	29 (23%)	..	..
Resection	..	..	1·12 (0·96–1·30)	0·17
No	33 (25%)	42 (33%)	..	..
Yes	99 (75%)	86 (67%)	..	..
Lymph-node infiltration	..	..	1·57 (1·06–2·33)	0·022
Yes or unresected	85 (64%)	99 (77%)	..	..
No	47 (36%)	29 (23%)	..	..
Resection margin infiltration	..	..	1·06 (0·83–1·35)	0·63
Yes or unresected	65 (49%)	62 (48%)	..	..
No	67 (51%)	66 (52%)	..	..
Intraoperative or early postoperative metastases	..	..	1·07 (1·01–1·14)	0·034
Yes	6 (5%)	15 (12%)	..	..
No	126 (95%)	113 (88%)	..	..
Clavien–Dindo classification†	..	..	..	..
Missing	2/99 (2%)	2/86 (2%)	..	..
0	7/97 (7%)	5/84 (6%)	..	..
I	48/97 (49%)	29/84 (35%)	..	..
II	25/97 (26%)	34/84 (40%)	..	..
IIIa	12/97 (12%)	12/84 (14%)	..	..
IIIb	2/97 (2%)	1/84 (1%)	..	..
IVa	0	0	..	..
IVb	2/97 (2%)	3/84 (4%)	..	..
V	1/97 (1%)	0	..	..

(Table 2 continues on next page)

(Continued from previous page)

	PAXG (n=132)	mFOLFIRINOX (n=128)	Relative response increase (95% CI)	p value
Clavien–Dindo classification ≤II†	..	..	1·02 (0·89–1·17)	0·79
Missing	2/99 (2%)	2/86 (2%)	..	..
No	17/97 (18%)	16/84 (19%)	..	..
Yes	80/97 (82%)	68/84 (81%)	..	..
Recurrence pattern‡	..	..	..	..
Local	16/83 (19%)	24/100 (24%)	..	..
Liver	27/83 (33%)	31/100 (31%)	..	..
Peritoneum	13/83 (16%)	17/100 (17%)	..	..
Lung	11/83 (13%)	8/100 (8%)	..	..
Not resectable	5/83 (6%)	3/100 (3%)	..	..
CA19-9 increase	12/83 (14%)	21/100 (21%)	..	..
Other sites	13/83 (16%)	11/100 (11%)	..	..
Event distribution‡	..	..	..	..
Unresectable	5/83 (6%)	3/100 (3%)	..	..
Disease progression	25/83 (30%)	34/100 (34%)	..	..
CA19-9§	4/25 (16%)	9/34 (26%)	..	..
Disease recurrence	45/83 (54%)	55/100 (55%)	..	..
CA19-9§	8/45 (18%)	12/55 (22%)	..	..
Intra-operatory metastasis	4/83 (5%)	6/100 (6%)	..	..
Death	4/83 (5%)	2/100 (2%)	..	..

Data are as n (%) or n/N (%), unless otherwise stated. CA19–9=carbohydrate antigen 19-9. *Includes four complete pathological responses. †Percentages are calculated based on the resected population, excluding missing data. ‡Percentages are calculated based on patients who experienced an event at the time of analysis. §Number of patients experiencing disease progression or disease recurrence based on CA19-9 increase. A more detailed description of CA19-9-based events is reported in the appendix (p 17).

Table 2: **Analysis of secondary endpoints in the intention-to-treat population for both treatment groups**

	PAXG (n=132)			mFOLFIRINOX (n=128)			p value
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4	
Haematological toxicity							
Anaemia	42 (32%)	3 (2%)	0	30 (23%)	0	0	0·058
Neutrophil count decreased (neutropenia)	37 (28%)	47 (36%)	9 (7%)	34 (27%)	31 (24%)	6 (5%)	0·012
Platelet count decreased	30 (23%)	1 (1%)	0	28 (22%)	1 (1%)	0	0·87
Febrile neutropenia	0	3 (2%)	0	0	1 (1%)	1 (1%)	0·68
Non-haematological toxicity							
Fatigue	86 (65%)	10 (8%)	1 (1%)	81 (63%)	10 (8%)	0	0·67
Nausea	76 (58%)	6 (5%)	0	90 (70%)	8 (6%)	0	0·012
Peripheral neuropathy	54 (41%)	7 (5%)	0	82 (64%)	4 (3%)	0	0·0006
Paraesthesia	30 (23%)	3 (2%)	0	47 (37%)	1 (1%)	0	0·030
Diarrhoea	46 (35%)	3 (2%)	0	76 (59%)	7 (5%)	0	<0·0001
Fever	45 (34%)	0	0	43 (34%)	1 (1%)	0	0·96
Hand–foot syndrome	42 (32%)	4 (3%)	1 (1%)	2 (2%)	0	0	<0·0001
Abdominal pain	32 (24%)	2 (2%)	0	44 (34%)	3 (2%)	0	0·056
Decreased appetite	31 (23%)	3 (2%)	0	29 (23%)	0	0	0·56
Vomiting	30 (23%)	2 (2%)	1 (1%)	38 (30%)	5 (4%)	0	0·13
Constipation	30 (23%)	0	0	24 (19%)	0	0	0·43
Dysgeusia	29 (22%)	0	0	19 (15%)	1 (1%)	0	0·19
Pain	29 (22%)	0	0	32 (25%)	0	0	0·56
Rash	19 (14%)	0	0	4 (3%)	0	0	0·0014
Mucositis oral	14 (11%)	1 (1%)	0	28 (22%)	4 (3%)	0	0·0043
Nail toxicity	11 (8%)	2 (2%)	0	3 (2%)	0	0	0·012
Infusion-related reaction	7 (5%)	1 (1%)	0	4 (3%)	5 (4%)	0	0·75
AST or ALT increased	7 (5%)	4 (3%)	0	21 (16%)	9 (7%)	1 (1%)	0·0005
Cough	6 (5%)	0	0	13 (10%)	0	0	0·082
Infection*	11 (8%)	0	0	5 (4%)	2 (2%)	0	0·36
Biliary tract infection	2 (2%)	4 (3%)	0	2 (2%)	4 (3%)	0	0·96
Sepsis	0	5 (4%)	0	0	3 (2%)	1 (1%)	0·77
Cholecystitis	0	1 (1%)	0	0	2 (2%)	0	0·54
GGT increased	2 (2%)	0	0	9 (7%)	4 (3%)	0	0·0028

Data are as n (%). p value compares all grade toxicities. Grade 1–2 treatment-related adverse events with an incidence of at least 10% in either group and grade 3–4 events with an incidence of at least 1% in either group are shown. All events are listed in the appendix (pp 11–15). Adverse events include those reported from the first dose of the study drug up to 30 days after the last dose. One treatment-related death due to sepsis in the mFOLFIRINOX group was reported with the worst grade before death. AST=aspartate aminotransferase. ALT=alanine aminotransferase. GGT=gamma-glutamyl transferase. *Includes lung, urinary tract, and catheter-related infections.

Table 3: **Summary of adverse events in the intention-to-treat population**

Research in context

Evidence before this study

From Jan 1, 2000, to June 29, 2020, we searched PubMed using the terms ("pancreatic ductal adenocarcinoma") AND (("neoadjuvant chemotherapy" OR "neoadjuvant chemo-radiotherapy") AND ("resectable" OR "borderline resectable")), limited to the English language. We filtered by article type "clinical trial" and "meta-analysis". In this scenario few phase 2 randomised trials emerged, as PACT15 (surgery upfront plus adjuvant gemcitabine or PEXG [cisplatin, epirubicin, capecitabine, and gemcitabine] *vs* perioperative PEXG) and Prep02 (surgery upfront plus adjuvant S-1 *vs* S-1 perioperative) both suggested the benefit of a neoadjuvant approach compared with primary surgery and adjuvant chemotherapy for patients with resectable pancreatic ductal adenocarcinoma (PDAC). Nevertheless, at that time, the only available phase 3 study, PREOPANC-1, performed in a mixed resectable and borderline resectable population, did not show a benefit of neoadjuvant gemcitabine plus radiotherapy compared with upfront surgery. Afterwards, the long-term, mature results of the study, reported in 2022 (while CASSANDRA was already ongoing), showed that preoperative chemoradiotherapy significantly prolonged survival over surgery. Thus, PREOPANC-1 provided evidence endorsing a neoadjuvant approach in patients with resectable and borderline resectable disease. Since then, several meta-analyses and additional phase 2 randomised studies were reported: NEONAX (surgery upfront followed by AG [nab-paclitaxel and gemcitabine] adjuvant *vs* AG perioperative) in patients with resectable disease and ESPAC5 (surgery plus adjuvant gemcitabine *vs* either short-course neoadjuvant mFOLFIRINOX, gemcitabine plus capecitabine, or chemoradiotherapy) in patients with borderline resectable disease, confirming neoadjuvant and perioperative therapy as a standard in these two settings. Conversely the NORPAC-1 trial (surgery upfront followed by adjuvant chemotherapy with mixed regimens *vs* 2-month preoperative chemotherapy with mixed regimens followed by surgery and postoperative chemotherapy) did not show significant differences between groups. Similarly, the SWOGS1505 phase 2 trial (perioperative nab-paclitaxel plus gemcitabine *vs* mFOLFIRINOX) for patients with resectable disease and the PREOPANC-2 phase 3 trial (neoadjuvant chemoradiotherapy and mFOLFIRINOX) for patients with resectable or borderline resectable disease showed no difference across regimens.

Added value of this study

Overall, cumulative evidence before and during the CASSANDRA trial showed that neoadjuvant therapy is a suitable standard approach in both resectable and borderline resectable PDAC, without evident differences among mFOLFIRINOX, nab-paclitaxel plus gemcitabine, capecitabine plus gemcitabine, or chemoradiation. To date, CASSANDRA and PREOPANC-2 are the only phase 3 studies testing the efficacy of different regimens in the field of resectable and borderline resectable PDAC. The CASSANDRA trial showed superiority of the PAXG regimen over mFOLFIRINOX in the setting of preoperative treatment of resectable and borderline resectable PDAC. Our findings supported not only that PAXG prolongs event-free survival, but also that it increases the rate of disease control, carbohydrate antigen 19-9 response, pathological complete response, pathological IA and IB stages, and node-negative resections, and reduces the incidence of intra or early postoperative metastases. According to subgroup analysis, the treatment effect consistently favoured PAXG across all the subpopulations. Furthermore, the PAXG regimen did not increase treatment-related toxicity and caused a clinically meaningful deterioration of quality of life in a smaller number of domains compared with mFOLFIRINOX.

Implications of all the available evidence

Neoadjuvant therapy should be indicated as standard-of-care for patients with non-metastatic PDAC before surgery. CASSANDRA sets PAXG as a new standard regimen for preoperative treatment of patients with resectable and borderline resectable PDAC.

Acute severe pain syndromes are medical conditions characterized by the sudden onset of intense, debilitating pain, often disproportionate to an underlying injury. While acute pain typically serves as a protective warning signal, these syndromes involve complex nervous system malfunctions that may transition into chronic conditions if not treated early.

What do give in the ambulance?
What if IV does not work?

Acute pain:

- Comes on quickly
- Caused by injury, surgery or illness
- Lasts six months or less
- Goes away when cause is addressed/treated

Chronic pain:

- Long-lasting and persistent
- Nerves become overactive or hypersensitive
- Lasts six months or more
- Treatment is complex and relief may be elusive

Comparison of inhalational methoxyflurane, intranasal fentanyl, and intravenous morphine for treatment of prehospital acute pain in Norway (PreMeFen): a randomised, non-inferiority, three-arm, phase 3 trial

Summary

Background Adequate pain control is essential; however, acute pain is often undertreated in prehospital care. This study aimed to evaluate three analgesic regimens for treating acute pain in an ambulance setting.

Methods PreMeFen is a randomised, open-label, non-inferiority, three-arm, phase 3 trial conducted in the working areas of the ground ambulance service of the Innlandet Hospital Trust, Norway. Patients aged 18–69 years and 70 years and older with traumatic or medical acute pain scoring 4 or higher on the Numeric Rating Scale (NRS) were randomly assigned (1:1:1) to receive in titration doses 3 mL inhalational methoxyflurane, 50 µg or 100 µg intranasal fentanyl, or 0·05 mg/kg or 0·1 mg/kg intravenous morphine, respectively, depending on the age group. The primary endpoint was change in pain NRS score from baseline to 10 min after treatment start and was analysed per protocol. The non-inferiority margin was 1·3. This trial is registered with ClinicalTrials.gov (NCT05137184) and is completed.

Findings Between Nov 12, 2021, and April 22, 2023, 632 patients were assessed for eligibility, and 338 were randomly assigned to methoxyflurane (n=112), fentanyl (n=115), or morphine (n=111). 281 patients were included in the per-protocol population. 145 (52%) of 281 patients were female and 136 (48%) were male. Median age was 61 years (IQR 47–75). The baseline NRS score was 7·6 (SD 1·8). Mean NRS score changes after 10 min were –3·31 (SD 2·67) for methoxyflurane, –1·98 (2·28) for fentanyl, and –2·74 (2·12) for morphine. Comparing changes in mean NRS score while adjusting for baseline showed that methoxyflurane was non-inferior to fentanyl (–1·33 [95% CI –2·01 to –0·64]) and morphine (–0·36 [–1·03 to 0·31]). Intranasal fentanyl was not non-inferior to morphine at 10 min (0·91 [0·27 to 1·55]). Adverse events occurred in 26 (24%) of 109 patients in the morphine group, 27 (24%) of 112 in the fentanyl group, and 24 (22%) of 111 in the methoxyflurane group. Two serious adverse events, respiratory depression (grade 2) and loss of consciousness (grade 3), occurred in the same patient in the methoxyflurane group. There were no treatment-related deaths.

Interpretation Inhalational methoxyflurane is non-inferior to intranasal fentanyl and intravenous morphine for acute pain management in the prehospital environment, assessed 10 min after administration. Inhalational methoxyflurane serves as a valuable non-intravenous alternative in the early phase of treatment and might bridge the gap to longer-acting analgesics.

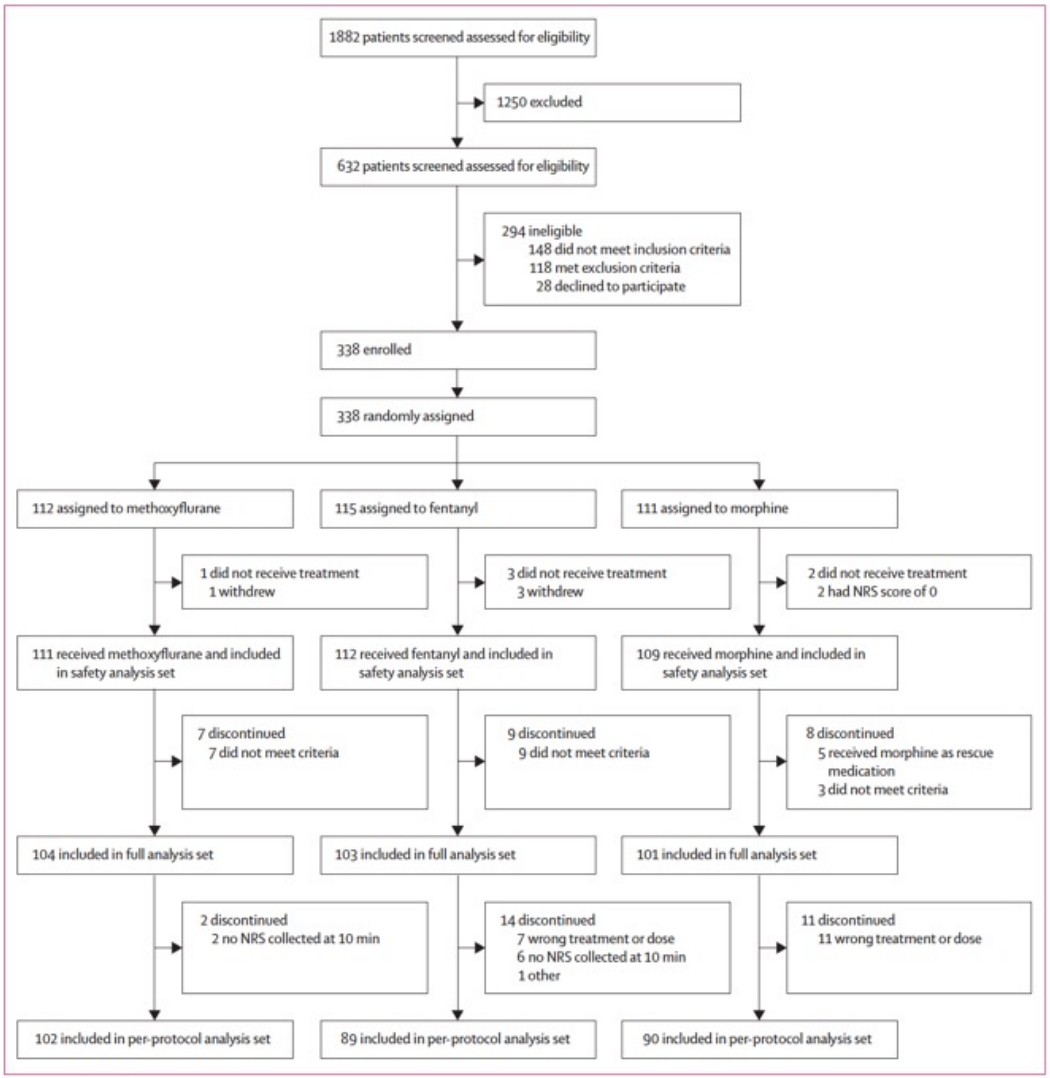


Figure 1: **Trial profile**
NRS=Numeric Rating Scale.

	Morphine group (n=90)	Fentanyl group (n=89)	Methoxyflurane group (n=102)
Sex			
Male	38 (42%)	47 (53%)	51 (50%)
Female	52 (58%)	42 (47%)	51 (50%)
Age, years	64 (48–76)	61 (50–75)	60 (47–74)
Weight, kg			
Median	76 (68–92)	80 (73–93)	81 (70–90)
Missing	1 (1%)	4 (4%)	9 (9%)
Diagnosis category*			
Chest pain of cardiac origin	3 (3%)	5 (6%)	6 (6%)
Trauma or injury pain	35 (39%)	30 (34%)	29 (28%)
Non-traumatic musculoskeletal	18 (20%)	28 (31%)	28 (27%)
Other non-traumatic pain	34 (38%)	26 (29%)	39 (38%)
Systolic blood pressure, mm Hg	150 (23·2)	153 (25·5)	151 (24·3)
Diastolic blood pressure, mm Hg	86 (17·8)	86 (14·3)	84 (15·2)
Pulse rate, min^{-1}	80 (70–94)	80 (70–93)	80 (69–89)
Respiratory rate, min^{-1}	18 (16–20)	18 (16–20)	18 (16–20)
Oxygen saturation			
Median	97% (95–99)	98% (96–99)	97% (96-99)
Missing	0	0	1 (1%)
Glasgow Coma Scale	15 (15–15)	15 (15–15)	15 (15–15)
Numeric Rating Scale	7 (5–9)	8 (7–9)	8 (6–9)

Data are n (%), median (IQR), or mean (SD). Baseline data were collected during screening. There were no missing data for variables unless included in the table. *Full diagnosis overview is provided in the appendix (p 15).

Table: **Demographic and baseline characteristics of the per-protocol population**

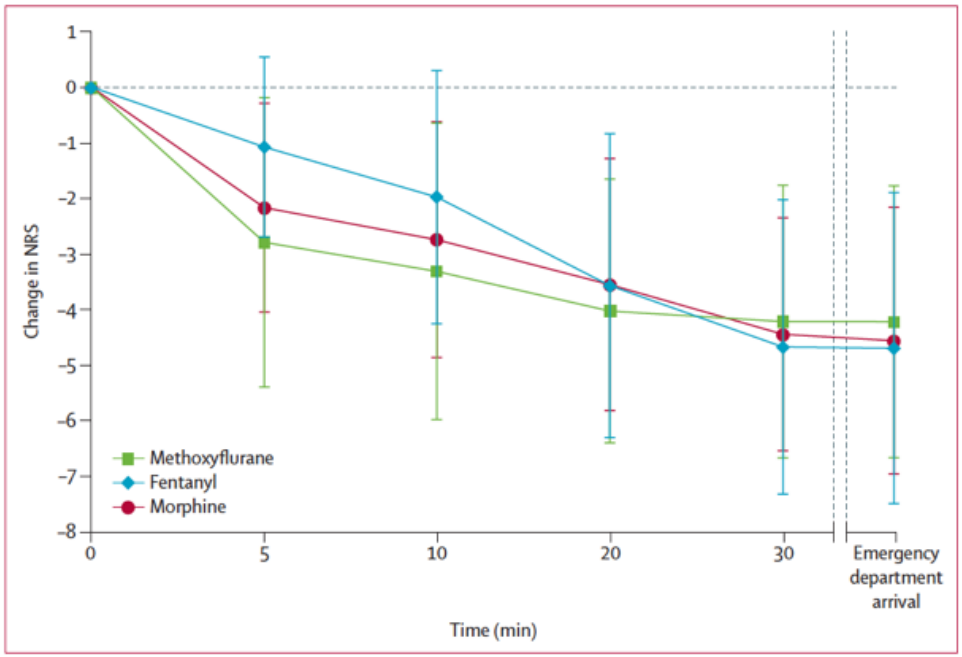


***Figure 2*: Pain relief efficacy measured by change in NRS score over time**
The figure shows the change in mean pain NRS score for morphine (red), fentanyl (blue), and methoxyflurane (green). Timepoints are time since administration of study medication. Lines represent mean change, and bars represent change by 1 SD. NRS=Numeric Rating Scale.

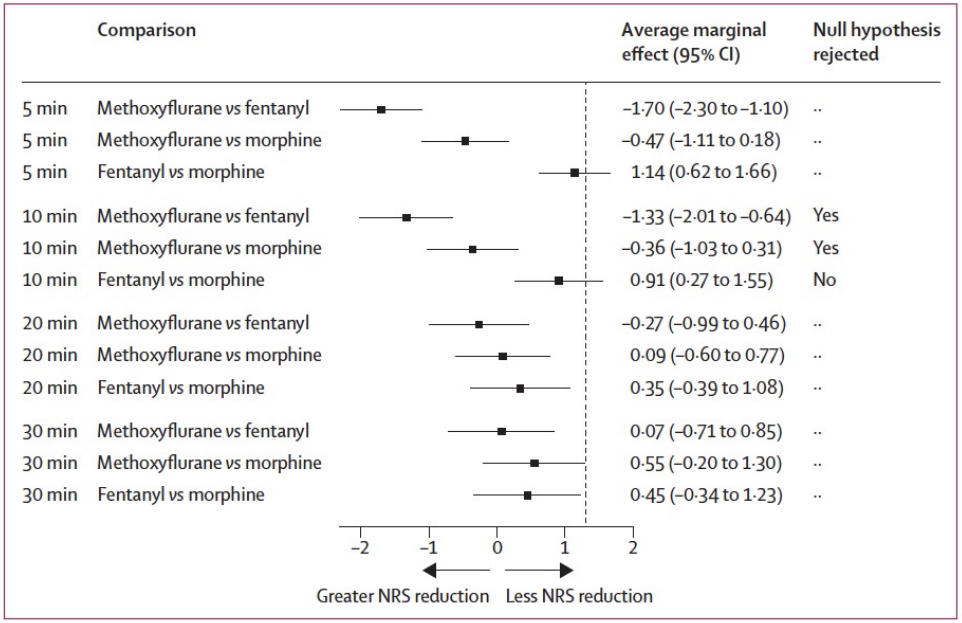


Figure 3: **Estimated difference in NRS score between treatment groups in the per-protocol analysis set**
The average marginal effect is measured across all observations using a balanced grid of covariates (if applicable). Change in NRS score at 10 min is the primary outcome. The other timepoints are secondary outcomes. For each timepoint, hypotheses 1–3 were tested sequentially and therefore no further adjustment for multiple testing were done. The dashed line represents the non-inferiority margin. NRS=Numeric Rating Scale.

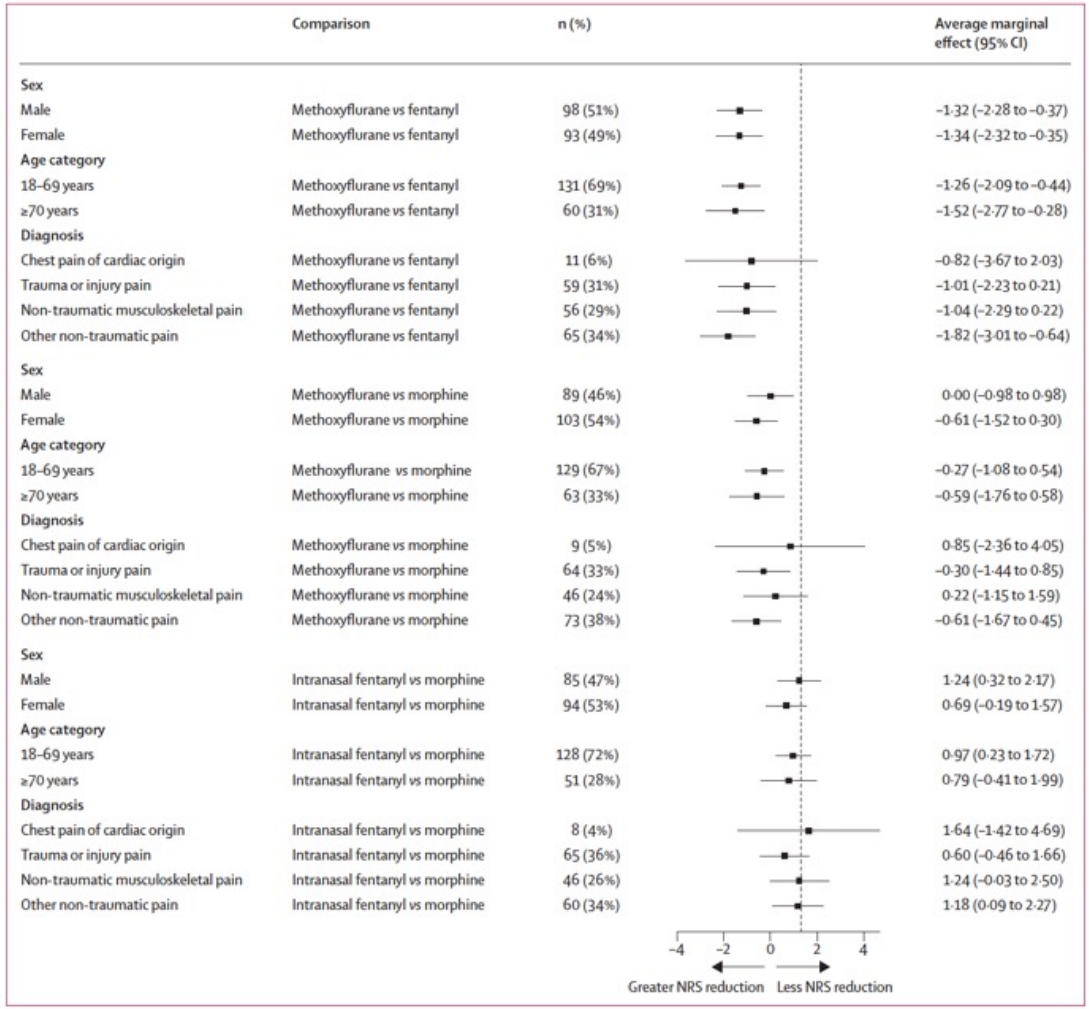


Figure 4: **Subgroup analysis 10 min after first dose of study drug**

The average marginal effect is measured across all observations using a balanced grid of covariates (if applicable). Differences in change in NRS score 10 minutes after first study drug dose between treatment groups, stratified by subgroups, using the per-protocol analysis set. The dashed line represents the non-inferiority margin. NRS=Numeric Rating Scale.

Research in context

Evidence before this study

We searched PubMed with the search terms ("fentanyl" OR "methoxyflurane") AND ("intranasal" OR "inhalation") AND ("emergency department" OR "emergency medical services" OR "ambulance" OR "air ambulance" OR "prehospital" OR "pre-hospital") AND ("acute pain" OR "pain management" OR "pain treatment" OR "pain therapy" OR "analgesia") for studies published between June 1, 2006, and June 1, 2021, later updated to June 1, 2025. We focused on clinical studies, clinical trials, randomised controlled trials, reviews, systematic reviews, and meta-analyses. A systematic review indicated that intranasal fentanyl and intravenous morphine have similar analgesic effects, as measured by changes in the Numeric Rating Scale, within pre-hospital settings. However, the quality of evidence was low, and studies did not assess time-to-effect. Methoxyflurane has shown significantly inferior analgesic efficacy compared with opioids at typical doses, but due to its rapid onset of action it might be valuable for immediate pain management when intravenous access is challenging. A large retrospective analysis showed that intranasal fentanyl and intravenous morphine were more efficacious than methoxyflurane, with no difference between fentanyl and morphine, but time-to-effect again was not assessed. Therefore, robust evidence comparing methoxyflurane, intranasal fentanyl, and intravenous morphine for immediate pain relief in prehospital care is scarce, and no clinical trial has directly performed this comparison.

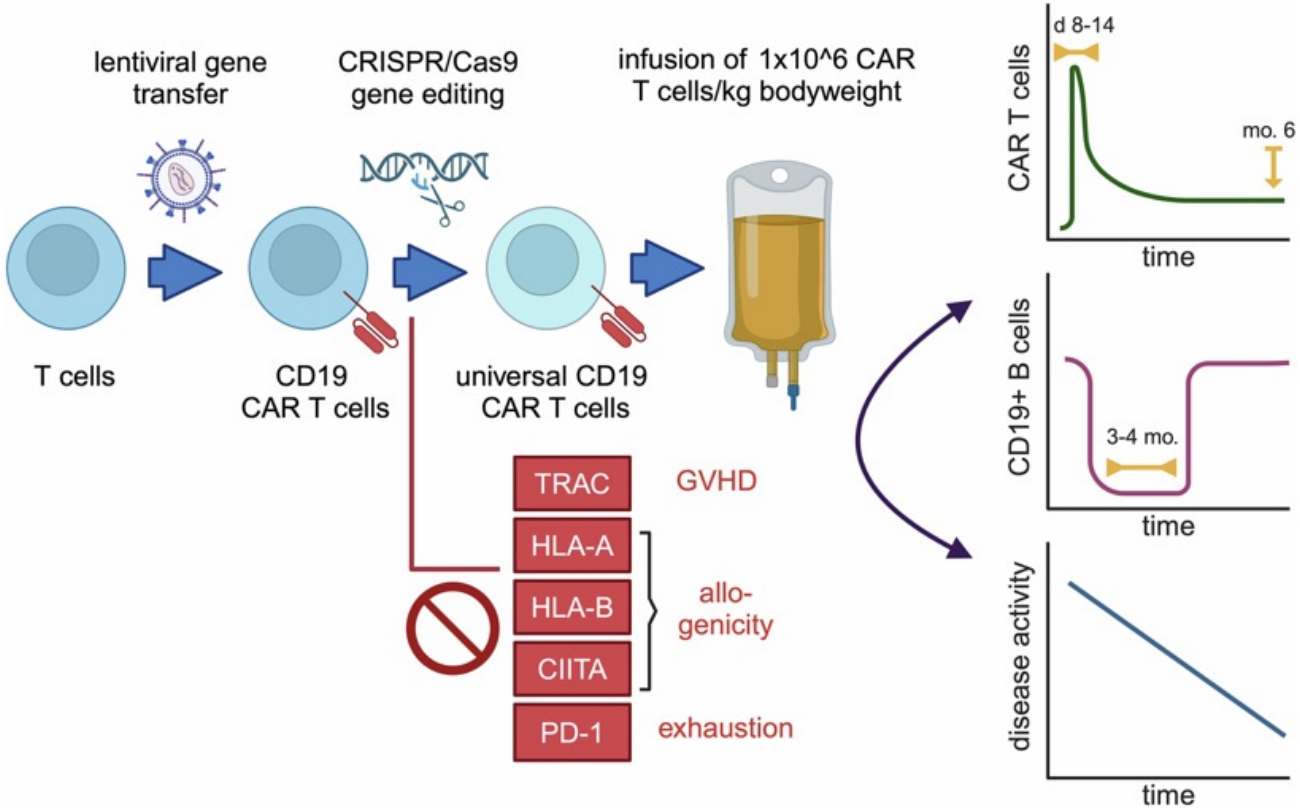
Added value of this study

The PreMeFen study contributes to the literature by establishing that methoxyflurane is non-inferior to intravenous morphine and intranasal fentanyl in the management of acute, moderate to severe traumatic and non-traumatic pain within the prehospital context, as assessed 10 min post-administration. Notably, while intranasal fentanyl did not show non-inferiority to intravenous morphine at 10 min, it was shown to be non-inferior at 20 min and 30 min. This study adds to existing evidence of non-intravenous alternatives for immediate pain relief in prehospital settings, offering real-world insights into analgesic regimens pertinent to ambulance and emergency care environments. To our knowledge, this study represents the first randomised trial comparing these three treatment regimens.

Implications of all the available evidence

Methoxyflurane and intranasal fentanyl are non-intravenous alternatives to morphine, which are available and show effectiveness for prompt pain relief in prehospital scenarios, with few serious adverse events. Our findings suggest that methoxyflurane serves as a useful non-intravenous alternative in the initial phase in which immediate pain relief is crucial and intravenous access remains unestablished. Furthermore, it acts as a bridge to longer-acting analgesics. Intranasal fentanyl necessitates a longer time frame to achieve its analgesic effect, establishing its non-inferiority to intravenous morphine after 20 min.

Allogeneic CAR T cells (also known as "off-the-shelf" CAR T) are genetically engineered immune cells derived from **healthy third-party donors** rather than the patient themselves. This approach aims to provide immediate, standardized, and more affordable treatment compared to personalized autologous therapies.



Efficacy and safety of allogeneic CD19 CAR NK-cell therapy in systemic lupus erythematosus: a case series in China

Summary

Background Lately, autologous CD19-targeting chimeric antigen receptor (CAR) T cells have shown excellent efficacy in treatment of autoimmune diseases, but with great safety concerns, such as infections. In this study, we aimed to evaluate the safety, tolerability, and efficacy of allogeneic CD19 CAR natural killer (NK)-cell therapy in patients with relapsed or refractory systemic lupus erythematosus (SLE).

Methods In this open-label, single-arm, prospective, first-in-human case series, we evaluated allogeneic CD19 CAR NK-cell therapy in adult patients (aged 18–65 years) with relapsed or refractory SLE at one site in China. Patients who had received at least two previous standard systemic therapies and continued to exhibit moderate-to-severe disease activity were eligible for inclusion. This study consisted of schedule escalation and dose escalation, with schedule escalation from 7 days and dose escalation commencing at $0{\cdot}75\times10^9$ CAR NK cells on day 0. All patients received a lymphodepleting conditioning regimen with fludarabine (25 mg/m² per day) and cyclophosphamide (300 mg/m² per day) administered daily from days –5 to –3, followed by three CAR NK-cell infusions within a single treatment cycle at identical dose levels and inter-infusion intervals. Dose-limiting adverse events were monitored in patients for 28 days. The primary endpoints of this study were safety and tolerability, including the incidence of dose-limiting toxicities and adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. This study was registered with ClinicalTrials.gov (NCT06010472) and follow-up is ongoing.

Findings 18 patients with relapsed or refractory SLE with moderate-to-severe disease activity were enrolled between Aug 21, 2023, and June 16, 2024. Of the 18 patients, 17 (94%) were female; the median age was 37·5 years (IQR 32·0–39·8), and the median disease duration was 10·5 years (IQR 4·5–14·8). Patients had received at least two standard systemic therapies, including biological agents (belimumab and telitacicept) in 14 (78%) of 18 patients, and plasmapheresis in one patient. Cytokine release syndrome was reported in one (6%) of 18 patients (grade 1). Neurotoxicity and other CAR NK-cell therapy-related severe adverse events were not observed, and there were no dose-limiting toxicities. Of the nine patients with more than 12 months' follow-up, six (67%) attained DORIS remission and lupus low disease activity state.

Interpretation This study suggests that allogeneic CAR NK-cell therapy is a potent option for treatment of autoimmune diseases and indicates that such a therapy might address limitations of current autologous CAR T-cell therapy, including manufacturing scale and time, access, safety, and cost.

DORIS (Definition of Remission In SLE) remission in Systemic Lupus Erythematosus is a specific, evidence-based definition from an international task force, meaning the patient has **no clinical lupus activity (clinical SLEDAI=0)**, a **very low physician's global score (<0.5)**, and is on minimal or no corticosteroids (prednisone ≤5 mg/day), while still potentially using stable doses of antimalarials, immunosuppressants, or biologics. It signifies a major treatment goal, allowing some medications for control but ensuring no active lupus symptoms, aiming to prevent long-term organ damage.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18
Patient characteristics																		
Age, years	23	42	30	37	38	32	37	41	39	24	40	37	43	19	39	48	38	32
Sex	Female	Female	Male	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female
Disease duration, years	6	7	14	15	15	1	6	10	15	3	11	2	17	11	11	1	1·8	16
Baseline SLEDAI-2K score*	14	9	12	13	28	11	14	12	16	8	14	12	10	10	14	10	8	8
Autoantibodies																		
Lead	..	..	dsDNA	dsDNA	dsDNA	..	dsDNA	dsDNA	dsDNA	dsDNA	dsDNA	dsDNA	..	dsDNA	dsDNA	..	..	dsDNA
Co-lead	..	Sm	..	..	Sm	NUC	..	..	..	..	Sm	..	..	..	NUC	..	..	Sm, NUC
Other	SSA, Ro-52	Ro-52, SSA	..	Ro-52, SSA	SSA, SSB, SCL-70	SSA, Ro-52	Ro-52, SSA	Ro-52, SSA, SSB	SSA	..	SSA	Ro-52, SSA	Ro-52	Ro-52, SSA, SSB	Ro-52, SSB	Ro-52, SSA	nRNP, rRNP, SSA	nRNP, rRNP, SSA
Organ involvement																		
Skin or mucosal	–	–	+	+	+	–	–	–	+	+	–	+	–	+	+	–	–	–
Kidney	+	–	+	–	+	+	+	–	+	–	–	–	–	–	–	+	–	+
Proteinuria	+	–	–	–	+	–	+	–	–	–	–	–	–	–	–	+	–	+
Haematuria	+	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–
Pyuria	–	–	+	–	+	+	–	–	+	–	–	–	–	–	–	+	–	–
Lung	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Bone marrow	–	+	–	+	–	+	+	+	–	+	–	–	+	–	–	–	–	–
Muscles and joints	+	+	–	+	–	+	–	+	+	–	–	+	+	+	+	–	+	–
Vascular	–	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–
Treatment																		
Glucocorticoids	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hydroxychloroquine	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–
Mycophenolate	+	–	–	+	+	+	+	+	–	–	+	+	–	+	+	–	+	+
Azathioprine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Cydophosphamide	+	–	+	+	+	–	+	–	–	–	–	–	–	–	+	+	–	+
Tacrolimus	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	+	+
Ciclosporin	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Rituximab	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Belimumab	+	+	+	+	+	+	+	–	–	–	–	+	–	+	+	+	–	–
Telitacicept	–	–	–	–	–	–	–	+	–	–	–	–	+	–	+	+	+	–
IVIg	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Other†	+	–	+	–	+	+	–	–	+	–	–	+	–	–	–	–	–	+

The + symbol indicates presence and the – symbol indicates absence. dsDNA=double-stranded DNA. IVIg=intravenous immunoglobulin. nRNP=nuclear ribonucleoprotein. NUC=nucleosome. rRNP=ribosomal ribonucleoprotein. SLE=systemic lupus erythematosus. SLEDAI-2k=Systemic Lupus Erythematosus Disease Activity Index 2000. Sm=Smith. SSA=Sjögren's-syndrome-related antigen A. SSB=Sjögren's-syndrome-related antigen B. *SLEDAI-2K score ranges from 0 to 105, with higher scores indicating greater disease activity. †Patient 1 received plasmapheresis; patient 3 received tofacitinib; patient 6 received methotrexate; and patients 5, 9, 12, and 18 received thalidomide.

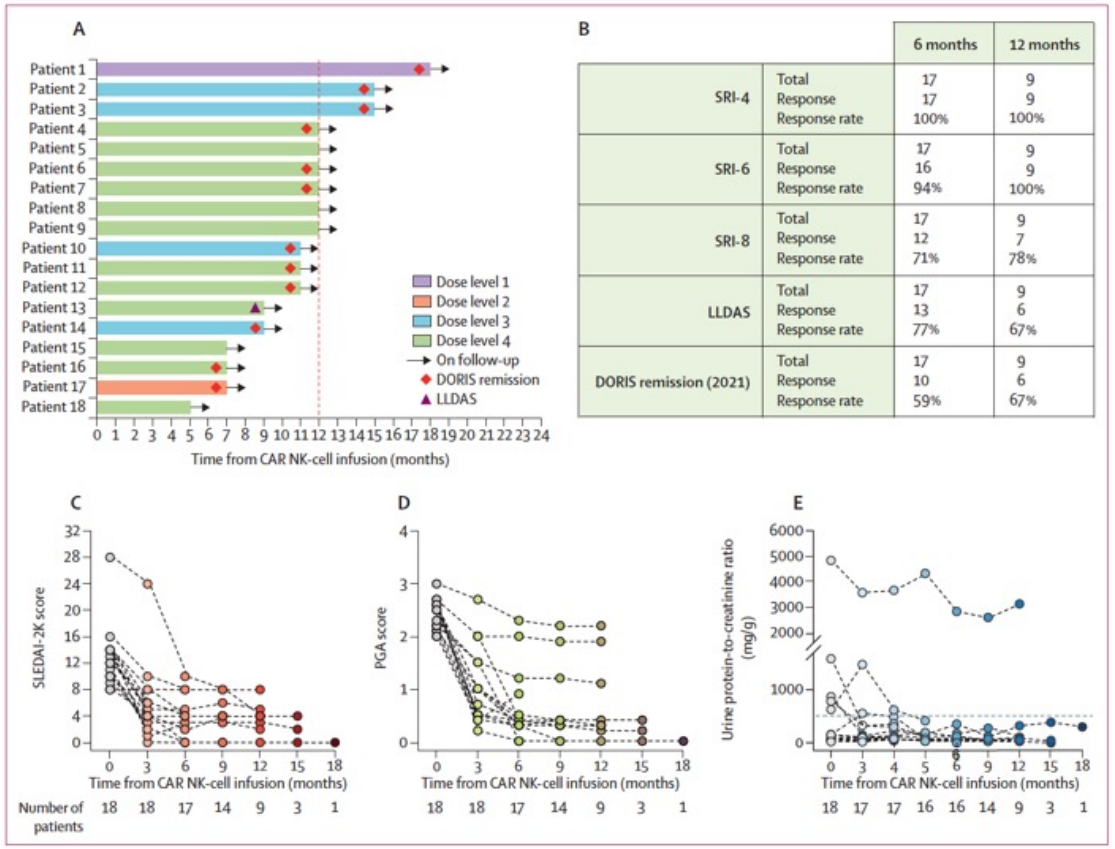
Table 1: Characteristics of 18 patients with SLE at baseline

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18
Infusion interval, days	7	7	7	5	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Dose level*	1	3	3	4	4	4	4	4	4	4	4	4	3	3	4	4	2	4
Follow-up, months	18	15	15	12	12	12	12	12	12	11	11	11	9	9	7	7	7	5
SLEDAI-2K score post-CAR NK-cell therapy†																		
0 months	14	9	12	13	28	11	14	12	16	8	14	12	10	10	14	10	8	8
6 months	0	3	4	4	10	3	4	5	8	4	4	4	0	2	8	0	2	NA
12 months	0	3	4	4	8	2	4	5	4	NA	NA	NA	NA	NA	NA	NA	NA	NA
Last follow-up	0	2	4	4	8	0	4	5	8	4	4	4	3	4	8	0	2	8
Glucocorticoids post-CAR NK-cell therapy‡																		
0 months	10 mg	7·5 mg	10 mg	10 mg	10 mg	5 mg	7·5 mg	10 mg	10 mg	3·75 mg	5 mg	5 mg	10 mg	10 mg	5 mg	10 mg	5 mg	10 mg
6 months	5 mg	5 mg	5 mg	5 mg	7·5 mg	5 mg	5 mg	10 mg	5 mg	3·75 mg	5 mg	5 mg	5 mg	5 mg	3·75 mg	5 mg	5 mg	NA
12 months	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	3·75 mg	10 mg	5 mg	NA	NA	NA	NA	NA	NA	NA	NA	NA
Last follow-up	5 mg	3·75 mg	5 mg	5 mg	5 mg	5 mg	3·75 mg	10 mg	5 mg	3·75 mg	5 mg	5 mg	5 mg	5 mg	3·75 mg	5 mg	5 mg	7·5 mg

CAR=chimeric antigen receptor. NA=not available. NK=natural killer. SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000. * Dose level 1: $0{\cdot}75 \times 10^9$ cells; dose level 2: $1{\cdot}5 \times 10^9$ cells; dose level 3: $3{\cdot}0 \times 10^9$ cells; dose level 4: $4{\cdot}5 \times 10^9$ cells. †SLEDAI-2K score ranges from 0 to 105, with higher scores indicating greater disease activity. ‡Prednisone-equivalent per day.

Table 2: **Summary of CAR NK-cell therapy information, follow-up, and outcomes**

Der **SLEDAI-2K** (Systemic Lupus Erythematosus Disease Activity Index 2000) ist ein klinischer Score zur Messung der Krankheitsaktivität bei Patienten mit Systemischem Lupus Erythematodes (SLE) innerhalb der letzten 10 Tage.



		6 months	12 months
SRI-4	Total	17	9
	Response	17	9
	Response rate	100%	100%
SRI-6	Total	17	9
	Response	16	9
	Response rate	94%	100%
SRI-8	Total	17	9
	Response	12	7
	Response rate	71%	78%
LLDAS	Total	17	9
	Response	13	6
	Response rate	77%	67%
DORIS remission (2021)	Total	17	9
	Response	10	6
	Response rate	59%	67%

Figure 1: **Clinical efficacy of allogeneic CD19 CAR NK-cell therapy**

(A) Follow-up and outcomes in patients with SLE after CD19 CAR-NK cell therapy (n=18). The coloured bars represent specific dose level groups: dose level 1 ($0{\cdot}75 \times 10^9$ CAR NK cells); dose level 2 ($1{\cdot}5 \times 10^9$ CAR NK cells); dose level 3 ($3{\cdot}0 \times 10^9$ CAR NK cells); and dose level 4 ($4{\cdot}5 \times 10^9$ CAR NK cells). The red dashed vertical line indicates the 12-month follow-up timepoint. (B) SRI response, LLDAS, and DORIS remission rates of patients who received CAR NK-cell therapy at 6-month and 12-month follow-up timepoints. (C–E) Outcomes of CD19 CAR NK-cell therapy in patients with SLE, including SLEDAI-2K scores (ranges from 0 to 105; increasing scores indicate more disease activity), PGA scores (ranges from 0 to 3; 0 indicates no disease activity, 3 indicates the most severe disease activity), and levels of urinary protein excretion at 3-month, 6-month, 9-month, 12-month, 15-month, and 18-month follow-up timepoints. For urinary protein excretion, the dashed horizontal line indicates the upper limit of the normal range. The protein-to-creatinine ratio was calculated with urinary protein measured in milligrams and urinary creatinine in grams. Each circle represents data from a single patient at a specific timepoint. Grey circles denote baseline data; circles of the same colour, with gradation from light to dark shades, represent data from different follow-up timepoints. CAR=chimeric antigen receptor. LLDAS=lupus low disease activity state. NK=natural killer. PGA=Physician Global Assessment. SLE=systemic lupus erythematosus. SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000. SRI=SLE Responder Index.

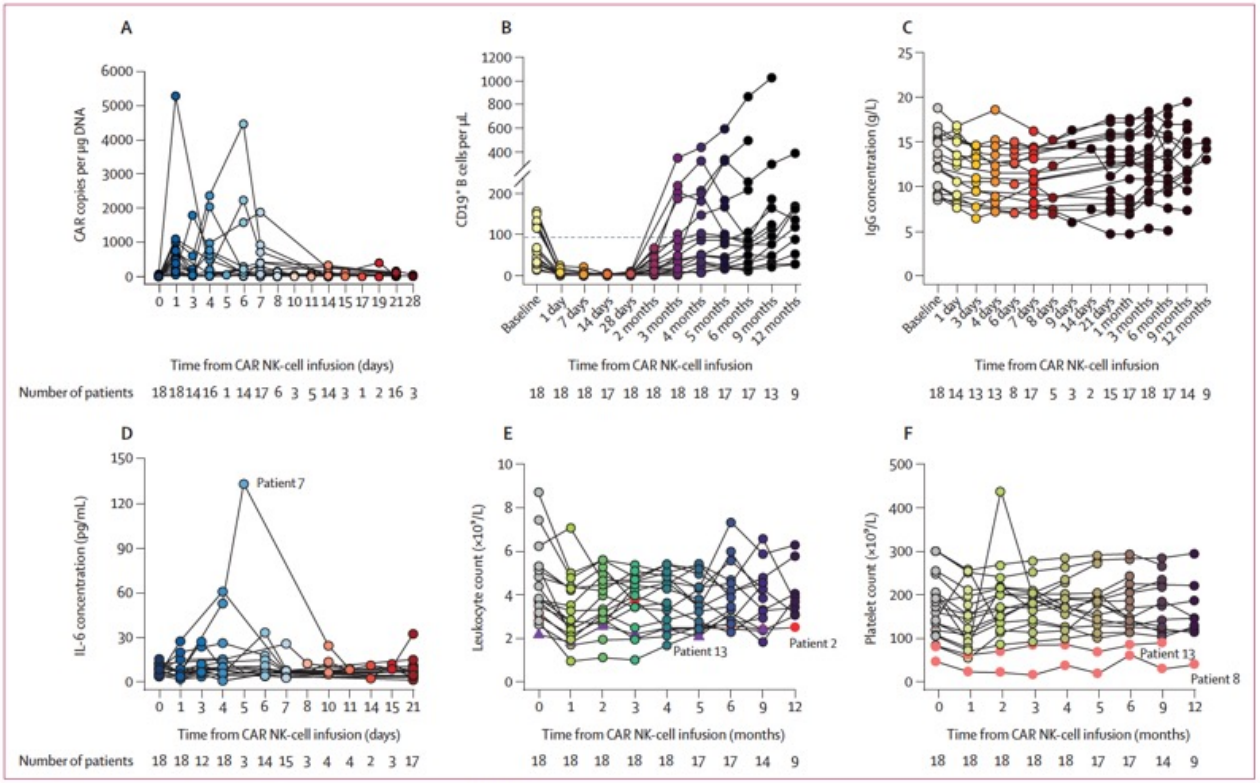


Figure 2: **Pharmacokinetics, pharmacodynamics, and safety profile of CAR NK-cell therapy**

In every graph in this figure, each circle represents data from an individual patient at a single timepoint, with distinct colours indicating different follow-up timepoints. (A) Quantitation of circulating CAR NK cells among total peripheral blood mononuclear cells at various days after CAR NK-cell treatment in 18 patients by quantitative real-time PCR. (B) Counts of $CD19^+$ B cells in peripheral blood of 18 patients with SLE at baseline and various days and months of follow-up after CAR NK-cell therapy. The dashed horizontal line represents the normal reference value. (C) IgG concentrations of 18 patients with SLE at baseline and various days and months of follow-up after CAR NK-cell therapy. (D–F) IL-6 concentrations, leukocyte counts, and platelet counts of 18 patients with SLE before and after lymphodepletion with cyclophosphamide and fludarabine, and treatment with CAR NK cells at baseline and follow-up. For the leukocyte counts, red circles denote data for patient 2 and purple triangles denote data for patient 13, as both of their leukocyte counts remained below the normal reference range by the last follow-up. For the platelet counts, light red circles denote data for patient 8 and patient 13, as both of their platelet counts remained below the normal reference range by the last follow-up. CAR=chimeric antigen receptor. NK=natural killer. SLE=systemic lupus erythematosus.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18
CRS	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–
ICANS	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Fatigue	–	–	+	+	–	+	+	+	+	+	–	–	–	–	–	–	+	–
Fever	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–
Decreased appetite	–	–	–	+	–	+	+	+	–	+	–	–	–	–	–	–	–	–
Nausea and vomiting	–	–	–	–	–	–	+	+	–	–	–	–	–	+	–	–	–	–
Diarrhoea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dizziness	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–
ALT increased	–	–	–	+	–	–	–	–	–	–	–	–	+	–	–	+	–	–
AST increased	–	+	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–
Bone marrow toxicity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Low IgG	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Tocilizumab treatment	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–

The + symbol indicates presence and the – symbol indicates absence. All listed adverse events were considered to be related to fludarabine–cyclophosphamide treatment apart from the CRS (and associated fever) in patient 7, which was related to CAR NK-cell therapy, and the fever in patient 6, which was related to bacterial upper respiratory tract infection. The CRS in patient 7 was grade 1, and the patient received tocilizumab 162 mg by hypodermic injection. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CAR=chimeric antigen receptor. CRS=cytokine release syndrome. ICANS=immune cell-associated neurotoxicity syndrome. NK=natural killer. SLE=systemic lupus erythematosus.

Table 3: **Short-term safety of CD19 CAR NK-cell therapy and fludarabine–cyclophosphamide treatment in patients with SLE**

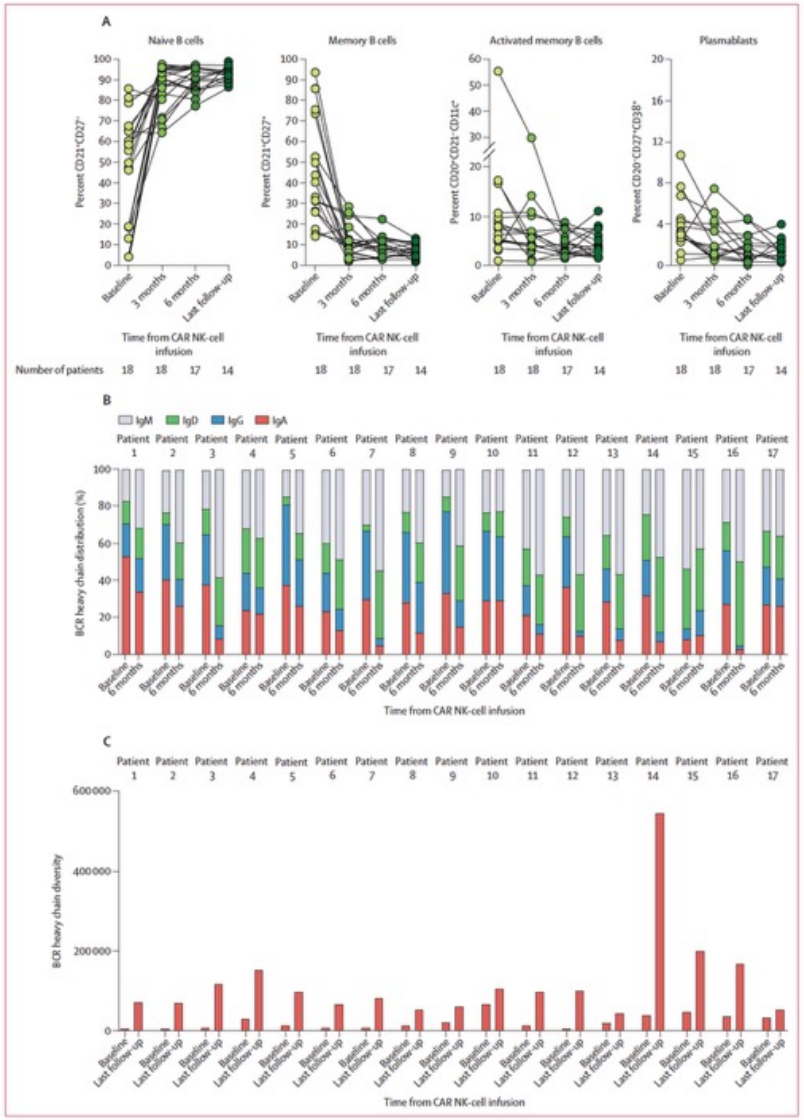


***Figure 3*: Reconstitution of B cells and BCR heavy chain distribution and diversity after CD19 CAR NK-cell treatment**

(A) Quantification of the percentage of naive B cells ($CD21^+CD27^-$), memory B cells ($CD21^+CD27^+$), activated memory B cells ($CD11c^+$), and plasmablasts ($CD20^+CD38^+$) between baseline (before CAR NK-cell infusion) and B-cell reconstitution at 3 months (n=18), 6 months (n=17), and the last follow-up timepoint (n=14) analysed by flow cytometry. Each circle represents data from an individual patient at a single timepoint, with distinct colours indicating different follow-up timepoints. (B-C) Assessment of heavy chain distribution and diversity in BCRs in 17 patients by high-throughput RNA sequencing at baseline and following CAR NK-cell therapy (6-month and last follow-up timepoints). BCR=B-cell receptor. CAR=chimeric antigen receptor. NK=natural killer.

Research in context

Evidence before this study

Autologous chimeric antigen receptor (CAR) T-cell therapy has shown the ability to produce meaningful long-term remission in patients with autoimmune diseases, but barriers impede widespread adoption in terms of limited manufacturing constraints and treatment accessibility, safety profiles requiring intensive monitoring, and prohibitive manufacturing costs. These challenges might be addressed by standardised allogeneic CAR-bearing cellular therapies. We searched PubMed on Feb 17, 2025, restricting to clinical trials published in any language and on any date, using the terms "autoimmune disease" AND "allogeneic" AND "chimeric antigen receptor". Only one publication on allogeneic CD19-targeted CAR T-cell therapy in one patient with severe myositis and two patients with systemic sclerosis was identified. This product was characterised by universal, healthy-donor-derived T cells, genetic engineering of multiple genes (*HLA-A*, *HLA-B*, *CIITA*, *TRAC*, and *PDCD1*) with CRISPR-Cas9, and lentivirus transduction of CAR. Furthermore, the allogeneic CD19-targeted universal CAR T cells showed tolerability, and achieved deep remission in patients with severe myositis and systemic sclerosis. This study supports the potential for allogeneic cell therapeutics to achieve meaningful efficacy in patients with autoimmune disease, but the broad applicability of these approaches remains unclear.

Added value of this study

To our knowledge, this study is the first-in-human trial of cord blood or peripheral blood-derived CAR natural killer (NK)-cell therapy in autoimmune disease. Allogeneic CD19 CAR NK cells were tolerable in patients with relapsed or refractory systemic lupus erythematosus and had favourable safety profiles with minimal cytokine release syndrome and no immune effector cell-associated neurotoxicity syndrome or other severe adverse events observed, allowing administration with off-the-shelf availability. Meanwhile, durable remissions were observed in this trial, indicating meaningful efficacy.

Implications of all the available evidence

Development of allogeneic cell therapies carries distinct advantages over autologous sources in autoimmune disease. Cord blood or peripheral blood-derived CAR NK-cell therapies are actively being studied in haematological malignancies and autoimmune diseases. Our trial indicates that this approach might address challenges with autologous CAR T-cell therapies, particularly in terms of safety files, manufacturing scalability constraints, and improving global treatment accessibility.

Amylin (auch **Insel-Amyloid-Polypeptid**, kurz IAPP) ist ein Peptidhormon, das gemeinsam mit Insulin in den Beta-Zellen der Bauchspeicheldrüse produziert und ausgeschüttet wird.

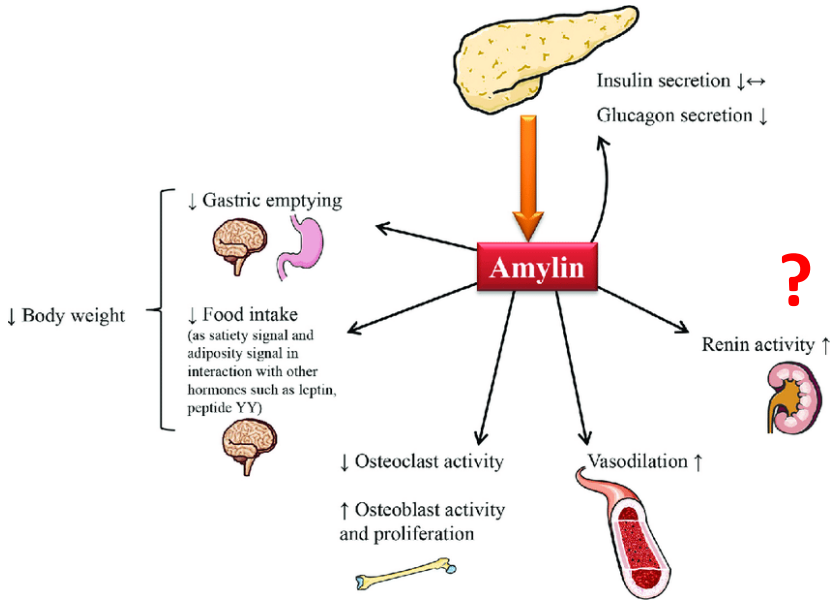
Funktionen und Wirkung
Im gesunden Körper unterstützt Amylin die Regulierung des Blutzuckerspiegels nach Mahlzeiten durch drei Hauptmechanismen:

- **Sättigungsgefühl:** Es wirkt direkt auf Sättigungszentren im Gehirn (insbesondere die *Area postrema*), um die Nahrungsaufnahme zu begrenzen.

- **Verzögerte Magenentleerung:** Es verlangsamt den Übertritt von Glukose aus der Nahrung ins Blut.

- **Glukagon-Hemmung:** Es unterdrückt die Ausschüttung von Glukagon, was die Glukosefreisetzung aus der Leber reduziert.

- **Renin Freisetzung** wird gesteigert.



Cagrilintid ist ein langwirksames, experimentelles Medikament, ein sogenanntes Amylin-Analog, das die Wirkung des natürlichen Hormons Amylin nachahmt und zur Appetitregulierung beiträgt, indem es das Sättigungsgefühl erhöht und die Magenentleerung verzögert. Es wird in der klinischen Entwicklung als Einzeltherapie und vor allem in Kombination mit dem GLP-1-Agonisten Semaglutid (als „CagriSema“) zur Gewichtsreduktion und zur Behandlung von Typ-2-Diabetes erforscht, mit vielversprechenden Ergebnissen in klinischen Studien.

Amylin and the renin-angiotensin system: risk or opportunity in amylin-based therapy?

We hypothesise that amylin receptor agonists (eg, pramlintide) and dual amylin and calcitonin-receptor agonists (eg, cagrilintide), which are emerging treatments for obesity and type 2 diabetes, can activate the renin-angiotensin system (RAS) and potentially undermine the cardiorenal benefits of these therapies. Paradoxically, new-generation amylin-based therapies, such as CagriSema, showed substantial blood pressure reductions in phase 3 trials. Beyond amylin's weight loss-mediated effects, we hypothesise that concurrent use of RAS inhibitors (angiotensin-converting enzyme [ACE] inhibitors or angiotensin-receptor blockers) redirects amylin-induced RAS activation towards the protective alternative RAS pathway, which is characterised by vasodilatory, anti-inflammatory, and antiproliferative effects via Mas receptors, potentially explaining part of their therapeutic benefit and cardioprotective and renoprotective potential. To test this, we propose: (1) preclinical studies investigating amylin–RAS interactions with or without RAS blockade; (2) post-hoc analyses of phase 2/3 trials stratified by RAS inhibitor use; (3) biomarker studies monitoring renin, aldosterone, angiotensin-(1–7), and ACE2; and (4) mechanistic human studies prospectively assessing cardiovascular–kidney metabolic effects by RAS inhibitor status. These suggestions aim to determine whether RAS inhibition enhances the overall efficacy of amylin-based therapies, and whether RAS blockers should be strongly recommended in patients receiving them.

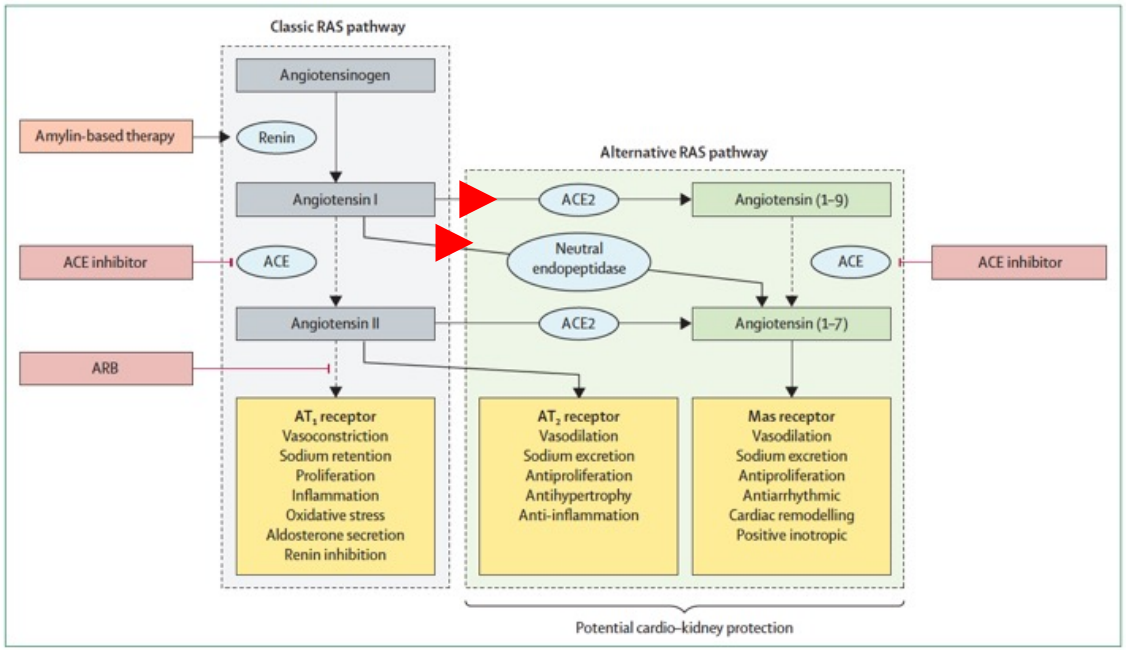


Figure: **Rationale for the potential benefit of combining amylin-based therapies with RAS inhibitors**
Combining amylin receptor agonists with ACE inhibitors or ARBs could improve cardiovascular and kidney outcomes by shifting RAS activity towards the increased stimulation of protective pathways such as the alternative RAS pathway involving AT_2 and Mas-receptors. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. AT_1=type 1 angiotensin II receptor. AT_2=type 2 angiotensin II receptor. RAS=renin-angiotensin system.

Conclusion

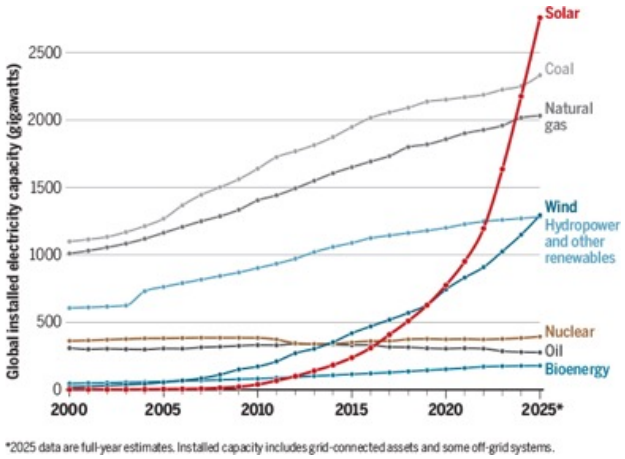
Amylin-based therapies represent a promising new drug class for obesity and type 2 diabetes care. Understanding the interaction of amylin-based therapies with the RAS and how this might be modulated by existing RAS inhibitor therapy could be pivotal in optimising the safety and efficacy of amylin-based treatments. We believe that this is a crucial and timely hypothesis that is deserving of targeted exploration in both preclinical and clinical domains, with the potential to refine treatment guidelines by labelling RAS inhibitor and amylin-based therapies as exploratory combination therapy needing further study, which prioritises precision-based combination therapy approaches and minimises polypharmacy to reduce complexity, cost, and adverse effects.

2025 BREAKTHROUGH OF THE YEAR

December 18, 2025

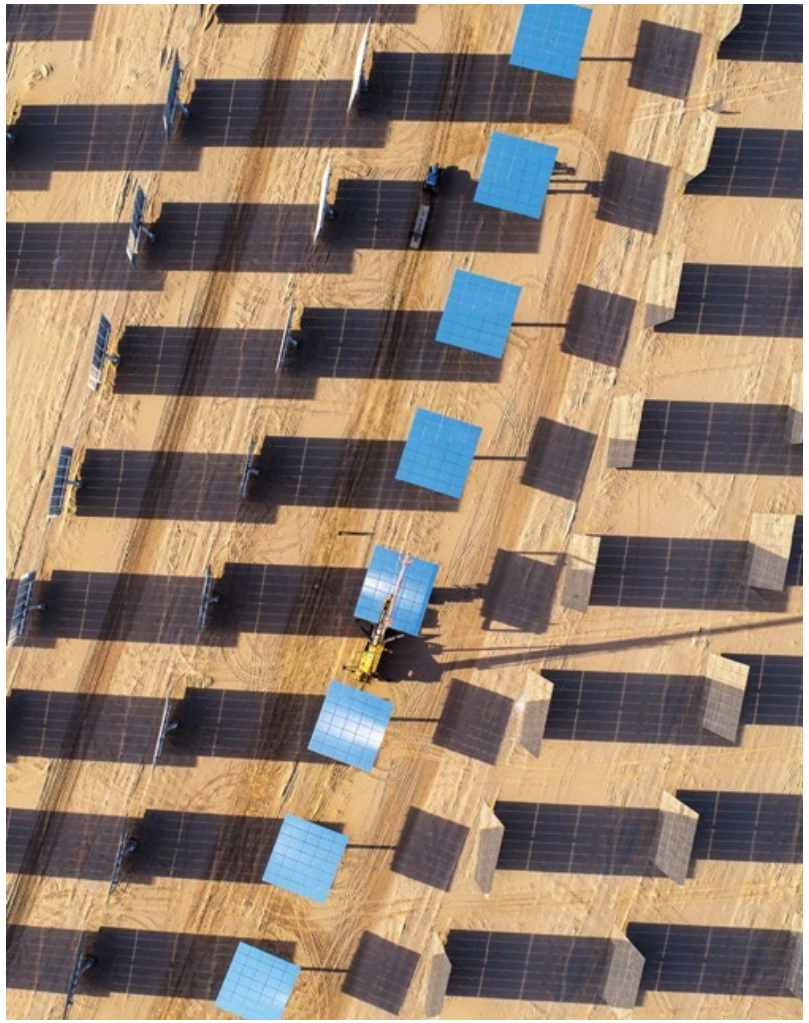
Good morning, sunshine

The seemingly unstoppable growth of renewable energy is *Science*'s 2025 Breakthrough of the Year



Aiming high Falling prices have propelled a surge in solar and wind energy that far outstrips the growth of any other source. This chart shows installed capacity, a comparison that favors solar and wind, which can produce at full power only a few hours a day, unlike fossil and nuclear. But renewable sources together generated more electricity this year than coal.

China's mighty industrial engine is the driver. After years of patiently nurturing the sector through subsidies, China now dominates global production of renewable energy technologies. It makes 80% of the world's solar cells, 70% of its wind turbines, and 70% of its lithium batteries, at prices no competitor can match. "China really mastered this … with the help of the scale of its economy, its manufacturing capacity, and the fierce competition right at home," says Li Shuo, director of the China Climate Hub at the Asia Society Policy Institute. As production surged, prices fell and demand took off. Production scaled up to keep pace, further driving down prices and igniting more demand. The result was a virtuous circle in which renewable technologies grew into an industry that now accounts for more than 10% of China's economy. Wind and solar became the cheapest energy in much of the world.



Tipped away from the Sun, a row of mirrors at China’s Shouhang Dunhuang concentrated solar power plant awaits servicing. Unlike solar panels, which generate power on their own, the plant’s 12,000 mirrors reflect sunlight to a central generating station

Kennedy Center board votes to rename to ‘Trump Kennedy Center’

Trustees voted to rename the center after President Donald Trump, who is also the board chair. Kennedy family members and Democrats blasted the move as illegal.

The board of the John F. Kennedy Center for the Performing Arts voted on Thursday to rename the storied arts institution the “Trump Kennedy Center,” an unprecedented change for the U.S. presidential memorial that drew swift condemnation from Kennedy family members and Democratic leaders.

The Kennedy Center confirmed the vote in an email to The Washington Post. The law establishing the building designates it as the John F. Kennedy Center for the Performing Arts.

“The Kennedy Center Board of Trustees voted unanimously today to name the institution The Donald J. Trump and The John F. Kennedy Memorial Center for the Performing Arts,” said Roma Daravi, the center’s vice president of public relations, in an email. “The unanimous vote recognizes that the current Chairman saved the institution from financial ruin and physical destruction.”

No joke!