ABSTRACT FROM CURRENT LITERATURE

Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

Wharton S, Blevins T, Connery L, et al

N Engl J Med 2023; 389: 877-888

Background: Obesity is a major risk factor for many leading causes of illness and death worldwide. Data are needed regarding the efficacy and safety of the nonpeptide glucagon-like peptide-1 (GLP-1) receptor agonist orforglipron as a once-daily oral therapy for weight reduction in adults with obesity.

Methods: In this phase 2, randomized, double-blind trial, we enrolled adults with obesity, or with overweight plus at least one weight-related coexisting condition, and without diabetes. Participants were randomly assigned to receive orforglipron at one of four doses (12, 24, 36, or 45 mg) or placebo once daily for 36 weeks. The percentage change from baseline in body weight was assessed at week 26 (primary end point) and at week 36 (secondary end point).

Results: A total of 272 participants underwent randomization. At baseline, the mean body weight was 108.7 kg. and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 37.9. At week 26, the mean change from baseline in body weight ranged from -8.6% to -12.6% across the orforglipron dose cohorts and was -2.0% in the placebo group. At week 36, the mean change ranged from -9.4% to -14.7% with orforglipron and was -2.3% with placebo. A weight reduction of at least 10% by week 36 occurred in 46 to 75% of the participants who received orforglipron, as compared with 9% who received placebo. The use of orforglipron led to improvement in all prespecified weight-related and cardiometabolic measures. The most common adverse events reported with orforglipron were gastrointestinal events, which were mild to moderate, occurred primarily during dose escalation, and led to discontinuation of orforglipron in 10 to 17% of participants across dose cohorts. The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class.

Conclusions: Daily oral orforglipron, a nonpeptide GLP-1 receptor agonist, was associated with weight reduction. Adverse events reported with orforglipron were similar to those with injectable GLP-1 receptor agonists. (Funded by Eli Lilly; GZGI ClinicalTrials.gov number, NCT05051579.

Trial of Endovascular Thrombectomy for Large Ischemic Strokes

Sarraj A, Hassan AE, Abraham MG, et al

N Engl J Med 2023; 388: 1259-1271

Background: Trials of the efficacy and safety of endovascular thrombectomy in patients with large ischemic strokes have been carried out in limited populations.

Methods: We performed a prospective, randomized, open-label, adaptive, international trial involving patients with stroke due to occlusion of the internal carotid artery or the first segment of the middle cerebral artery to assess endovascular thrombectomy within 24 hours after onset. Patients had a large ischemic-core volume, defined as an Alberta Stroke Program Early Computed Tomography Score of 3 to 5 (range, 0 to 10, with lower scores indicating larger infarction) or a core volume of at least 50 ml on computed tomography perfusion or diffusion- weighted magnetic resonance imaging. Patients were assigned in a 1:1 ratio to endovascular thrombectomy plus medical care or to medical care alone. The primary outcome was the modified Rankin scale score at 90 days (range, 0 to 6, with higher scores indicating greater disability). Functional independence was a secondary outcome.

Results: The trial was stopped early for efficacy; 178 patients had been assigned to thrombectomy and 174 to medical care. The median ischemic-core volumes were 74 ml and 77 ml in the two groups, respectively. The generalized odds ratio for a shift in the distribution of modified Rankin scale scores toward better outcomes in favor of thrombectomy was 1.51 (95% confidence interval [CI], 1.20 to 1.89; P<0.001). A total of 20% of the patients in the thrombectomy group and 7% in the medical-care group had functional independence (relative risk, 2.97; 95% CI, 1.60 to 5.51). Mortality was similar in the two groups. In the thrombectomy group, arterial access-site complications occurred in 5 patients, dissection in 10, cerebral-vessel perforation in 7, and transient vasospasm in 11. Symptomatic intracranial hemorrhage occurred in 1 patient in the thrombectomy group and in 2 in the medical-care group.

Conclusions: Among patients with large ischemic strokes, endovascular thrombectomy resulted in better functional outcomes than medical care but was associated with vascular complications. Cerebral hemorrhages were infrequent in both groups. (Funded by Stryker Neurovascular; SELECT2 ClinicalTrials.gov number, NCT03876457.)

An investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema: a two-part, randomised, double-blind, placebo-controlled, crossover phase 2 trial

Pürsün EA, Zanichelli A, Cohn DM, et al

The Lancet 2023; 401: 458-469

Background: Guidelines recommend effective on-demand therapy for all individuals with hereditary angioedema. We aimed to assess the novel oral plasma kallikrein inhibitor, sebetralstat, which is in development, for on-demand treatment of hereditary angioedema attacks.

Methods: In this two-part phase 2 trial, individuals with type 1 or 2 hereditary angioedema aged 18 years or older were recruited from 25 sites, consisting of specialty outpatient centres, across nine countries in Europe and the USA. Individuals were eligible if they had experienced at least three hereditary angioedema attacks in the past 93 days, were not on prophylactic therapy, and had access to and the ability to self-administer conventional attack treatment. In part 1 of the trial, participants were given a single 600 mg open-label oral dose of sebetralstat to assess safety, pharmacokinetics, and pharmacodynamics of the dose. Part 2 was a randomised, double-blind, placebo-controlled, two-sequence, two-period (2 x 2) crossover trial; participants were randomly assigned (1:1) to either sequence 1, in which they were given a single dose of 600 mg of sebetralstat to treat the first eligible attack and a second dose of placebo to treat the second eligible attack, or sequence 2, in which they were given placebo to treat the first eligible attack and then 600 mg of sebetralstat to treat the second eligible attack. Participants and investigators were masked to treatment assignment. The primary endpoint was time to use of conventional attack treatment within 12 h of study drug administration, which was assessed in all participants who were randomly assigned to treatment and who received study drug for two attacks during part 2 of the study. Safety was assessed in all participants who received at least one dose of study drug, starting in part 1. This study is registered with ClinicalTrials.gov, NCT04208412, and is completed.

Findings: Between July 2, 2019, and Dec 8, 2020, 84 individuals were screened and 68 were enrolled in part 1 and received sebetralstat (mean age 38.3 years [SD 13.2], 37 [54%] were female, 31 [46%] were male, 68 [100%] were White). 42 (62%) of 68 participants completed pharmacokinetic assessments. Sebetralstat was rapidly absorbed, with a geometric mean plasma concentration of 501 ng/mL at 15 min. In a subset of participants (n=6), plasma samples obtained from 15 min to 4 h after study drug administration had near-complete protection from ex vivo stimulated generation of plasma kallikrein and cleavage of high-molecular-weight kininogen. In part 2, all 68 participants were randomly assigned to sequence 1 (n=34) or sequence 2 (n=34). 53 (78%) of 68 participants treated two attacks (25 [74%] in the sequence 1 group and 28 [82%] in the sequence 2 group). Time to use of conventional treatment within 12 h of study drug administration was significantly longer with sebetralstat versus placebo (at quartile 1: >12 h [95% CI 9.6 to >12] vs 8.0 h [3.8 to >12]; p=0.0010). There were no serious adverse events or adverse event-related discontinuations.

Interpretation: Oral administration of sebetralstat was well tolerated and led to rapid suppression of plasma kallikrein activity. resulting in increased time to use of conventional attack treatment and faster symptom relief versus placebo. Based on these results, a phase 3 trial to evaluate the efficacy and safety of two dose levels of sebetralstat in adolescent and adult participants with hereditary angioedema has been initiated (NCT05259917).

Incidence, aetiology and neurodisability associated with severe microcephaly: a national surveillance study

Knowles RL, Solebo AL, Sampaio MA, et al

Archives of Disease in Childhood 2023;108:211-217

Objective: To determine the incidence, causes and neurodevelopmental impact of severe microcephaly (head circumference <-3SD) up to age 2 years.

Design: Binational active paediatric surveillance study undertaken in 2017-2018 to identify and characterise new diagnoses of severe microcephaly.

Setting: UK and Ireland.

Participants: Infants aged under 12 months at diagnosis.

Interventions: Observational study.

Main outcome measures: Incidence, aetiology and neurodevelopmental outcomes at age 2 years.

Results: Fifty-nine infants met the case definition, of whom 30 (51%) were girls; 24 (41%) were born preterm (<37 weeks' gestation); and 34 (58%) were of 'white' ethnicity. Eight (14%) children died before 12 months of age. Incidence of severe microcephaly was 5.5 per 100 000 infants (95% CI 4.0 to 7.3). Higher relative risk (RR) was associated with preterm birth (RR 7.7, 95% CI 3.8 to 15.1) and British Asian ethnicity (RR 3.6, 95% CI 1.6 to 7.8). Microcephaly was mainly due to genetic causes (59%), brain ischaemia/hypoxia (10%) and congenital infection (8%), and 19% remained undetermined. Each child was referred on average to eight specialists, and 75% had abnormal brain imaging. By 2 years of age, 55

children experienced neurodevelopmental abnormalities, including feeding problems (68%), motor delay (66%), visual impairment (37%), hearing loss (24%) and epilepsy (41%).

Conclusions: Although severe microcephaly is uncommon, it is associated with high mortality, complex multimorbidity and neurodisability, thus representing a significant ongoing burden for families and healthcare services. Potentially preventable causes include preterm birth, hypoxic/ischaemic brain injury and congenital infections. Clinical guidelines are essential to standardise aetiological investigation and optimise multidisciplinary management.

Strategies to avoid mastectomy skin-flap necrosis during nipple-sparing mastectomy

Moo TA and others

British Journal of Surgery 2023; 110: 831-838

Background: Nipple-sparing mastectomy is associated with a higher risk of mastectomy skin-flap necrosis than conventional skin-sparing mastectomy. There are limited prospective data examining modifiable intraoperative factors that contribute to skin-flap necrosis after nipple-sparing mastectomy.

Methods: Data on consecutive patients undergoing nipple-sparing mastectomy between April 2018 and December 2020 were recorded prospectively. Relevant intraoperative variables were documented by both breast and plastic surgeons at the time of surgery. The presence and extent of nipple and/or skin-flap necrosis was documented at the first postoperative visit. Necrosis treatment and outcome was documented at 8-10 weeks after surgery. The association of clinical and intraoperative variables with nipple and skin-flap necrosis was analysed, and significant variables were included in a multivariable logistic regression analysis with backward selection.

Results: Some 299 patients underwent 515 nipple-sparing mastectomies (54.8 per cent (282 of 515) prophylactic, 45.2 per cent therapeutic). Overall, 23.3 per cent of breasts (120 of 515) developed nipple or skin-flap necrosis; 45.8 per cent of these (55 of 120) had nipple necrosis only. Among 120 breasts with necrosis, 22.5 per cent had superficial, 60.8 per cent had partial, and 16.7 per cent had full-thickness necrosis. On multivariable logistic regression analysis, significant modifiable intraoperative predictors of necrosis included sacrificing the second intercostal perforator (P =0.006), greater tissue expander fill volume (P<0.001), and non-lateral inframammary fold incision placement (P = 0.003).

Conclusion: Modifiable intraoperative factors that may decrease the likelihood of necrosis after nipple-sparing mastectomy include incision placement in the lateral inframammary fold, preserving the second intercostal perforating vessel, and minimizing tissue expander fill volume.

Outcomes of Parastomal Hernia Repair After National Centralization

Helgstrand F and others

British Journal of Surgery 2023; 110: 60-66

Background: In 2010, it was decided to centralize parastomal hernia repairs to five specialized hernia centres in Denmark to improve outcomes. The aim of this nationwide cohort study was to evaluate whether centralization of parastomal hernia repairs has had an impact on outcomes. Specifically, readmission, reoperation for complication, and operation for recurrence were analysed before and after centralization.

Methods: By merging clinical and administrative outcome data from the Danish Hernia Database with those from the Danish National Patient Registry, all patients undergoing parastomal hernia repair in Denmark from 1 January 2007 to 31 December 2018 were included. Centralization was defined as having at least 70 per cent of procedures were performed at one of the five national centres. Readmission, reoperation, and recurrence rates for emergency and elective repairs were evaluated before and after centralization.

Results: In total, 1062 patients were included. Median follow-up was 992 days. Overall, the centralization process took 7 years. For elective repairs, the readmission, reoperation, mortality, and recurrence rates were comparable before and after centralization, but more patients overall and more patients with co-morbidity were offered surgery after centralization. For emergency repairs, there was a significant reduction in rates of reoperation (from 44.9 per cent (48 of 107) to 23 per cent (14 of 62); P = 0.004) and mortality (from 10.3 per cent (11 of 107) to 2 per cent (1 of 62); P = 0.034) after centralization.

Conclusion: Centralization led to more elective operations and better outcomes when emergency repair was needed. Centralization of parastomal hernia repair led to more patients receiving elective repair and significantly improved outcomes after emergency repair.

Arterial stiffness for the early prediction of pre-eclampsia compared with blood pressure, uterine artery Doppler and angiogenic biomarkers: a prospective cohort study

Phan K, Gomez YH, Gorgui J, et al

BJOG 2023; 130: 932-940

Objective: Our aim was to evaluate the ability of arterial stiffness parameters to predict pre-eclampsia early biomarkers compared with peripheral blood pressure, uterine artery Doppler and established angiogenic biomakers.

Design: Prospective cohort study. Setting Tertiary care antenatal clinics in Montreal, Canada. Population Women with singleton high-risk pregnancies.

Methods: In the first trimester, arterial stiffness was measured by applanation tonometry, along with peripheral blood pressure and serum/plasma angiogenic biomarkers; uterine artery Doppler was measured in the second trimester. The predictive ability of different metrics was assessed through multivariate logistic regression.

Main outcome measures: Arterial stiffness (carotid-femoral pulse wave velocity, carotid-radial pulse wave velocity) and wave reflection (augmentation index, reflected wave start time), peripheral blood pressure, ultrasound indices of velocimetry and circulating angiogenic biomarker concentrations.

Results: In this prospective study, among 191 high-risk pregnant women, 14 (7.3%) developed pre-eclampsia. A first-trimester 1 m/s increase in carotid-femoral pulse wave velocity was associated with 64% increased odds ($P<0.05$), and a 1-millisecond increase in time to wave reflection with 11% decreased odds for pre-eclampsia ($P<0.01$). The area under the curve of arterial stiffness, blood pressure, ultrasound indices and angiogenic biomarkers was 0.83 (95% confidence interval [CI] 0.74-0.92), 0.71 (95% CI 0.57-0.86), 0.58 (95% CI 0.39-0.77), and 0.64 (95% CI 0.44-0.83), respectively. With a 5% false-positive rate, blood pressure had a sensitivity of 14% for pre-eclampsia and arterial stiffness a sensitivity of 36%.

Conclusions: Arterial stiffness predicted pre-eclampsia earlier and with greater ability than blood pressure, ultrasound indices or angiogenic biomarkers.

Hormone replacement cycles are associated with a higher risk of hypertensive disorders: Retrospective cohort study in singleton and twin pregnancies

Pape J, Levy J, Wolff MV, et al

BJOG 2023; 130: 377-386

Objective: To elaborate the associations of different cycle regimens (natural cycle [NC], stimulated cycle [SC], hormone replacement cycle [HRC]) on maternal and neonatal adverse pregnancy outcomes after frozen-thawed embryo transfers (FET).

Design: Population-based registry study.

Setting: Swiss IVF Registry. Population or Sample: Singleton (n=4636) and twin (n = 544) live births after NC-FET (n=776), SC-FET (n = 758) or HRC-FET (n=3646) registered from 2014 to 2019.

Methods: Fifteen pregnancy pathologies were modelled for singleton and twin pregnancies using mixed models adjusted for cycle regimen, delivery, fertilisation technique, chronic anovulation, age of mother and centre.

Main outcome measures: Maternal (vaginal bleeding, isolated arterial hypertension and pre-eclampsia) and neonatal (gestational age, birthweight, mode of delivery) adverse pregnancy outcomes.

Results: In singleton pregnancies, the incidences of bleeding in first trimester, isolated hypertension and pre-eclampsia were highest in HRC-FET with doubled odds of bleeding in first trimester (adjusted odds ratio [OR] 2.23; 95% CI 1.33-3.75), isolated hypertension (aOR 2.50; 95% CI 1.02-6.12) and pre-eclampsia (aOR 2.16; 95% CI 1.13-4.12) in HRC-FET vs. NC-FET and with doubled respectively sixfold odds of bleeding (aOR 2.08; 95% CI 1.03-4.21) and pre-eclampsia (6.02; 95% CI 1.38-26.24) in HRC-FET versus SC-FET. In twin pregnancies, the incidence of pre-eclampsia was highest in HRC-FET with numerically higher odds of pre-eclampsia in HRC-FET versus NC-FET and versus SC-FET.

Conclusions: Our data implied the highest maternal risks of hypertensive disorders in HRC-FET, therefore clinicians should prefer SC-FET or NC-FET if medically possible.