Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial --

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Summary

Background

Fibroblast growth factor 21 (FGF21) regulates metabolism and protects cells against stress. Efruxifermin is a bivalent Fc–FGF21 analogue that replicates FGF21 agonism of fibroblast growth factor receptor 1c, 2c, or 3c. The aim of this phase 2b study was to assess its efficacy and safety in patients with non-alcoholic steatohepatitis (NASH) and moderate (F2) or severe (F3) fibrosis.

Methods

HARMONY is a multicentre, randomised, double-blind, placebo-controlled, 96-week, phase 2b trial that was initiated at 41 clinics in the USA. Adults with biopsy-confirmed NASH, defined by a non-alcoholic fatty liver disease activity score (NAS) of 4 or higher and scores of 1 or higher in each of steatosis, ballooning, and lobular inflammation, with histological stage F2 or F3 fibrosis, were randomly assigned (1:1:1), via an interactive response system, to receive placebo or efruxifermin (28 mg or 50 mg), subcutaneously once weekly. Patients, investigators, pathologists, site staff, and the sponsor were masked to group assignments during the study. The primary endpoint was the proportion of patients with improvement in fibrosis of at least 1 stage and no worsening of NASH, based on analyses of baseline and week 24 biopsies (liver biopsy analysis set [LBAS]). A sensitivity analysis evaluated the endpoint in the full analysis set (FAS), for which patients with missing biopsies were considered non-responders. This trial is registered with ClinicalTrials.gov, NCT04767529, and is ongoing.

Findings

Between March 22, 2021, and Feb 7, 2022, 747 patients were assessed for eligibility and 128 patients (mean age 54·7 years [SD 10·4]; 79 [62%] female and 49 male [38%]; 118 [92%] white; and 56 [41%] Hispanic or Latino) were enrolled and randomly assigned to receive placebo (n=43), efruxifermin 28 mg (n=42; two randomised patients were not dosed because of an administrative error), or efruxifermin 50 mg (n=43). In the LBAS (n=113), eight (20%) of 41 patients in the placebo group had an improvement in fibrosis of at least 1 stage and no worsening of NASH by week 24 versus 15 (39%) of 38 patients in the efruxifermin 28 mg group (risk ratio [RR] 2·3 [95% CI 1·1–4·8]; p=0·025) and 14 (41%) of 34 patients in the efruxifermin 50 mg group (2·2 [1·0–5·0]; p=0·036). Based on the FAS (n=128), eight (19%) of 43 patients in the placebo group met this endpoint versus 15 (36%) of 42 in the efruxifermin 28 mg group (RR 2·2 [95% CI 1·0–4·8]; p=0·033) and 14 (33%) of 43 in the efruxifermin 50 mg group (1·9 [0·8–4·3]; p=0·123). The most frequent efruxifermin-related adverse events were diarrhoea (16 [40%] of 40 patients in the efruxifermin 28 mg group and 17 [40%] of 43 patients in efruxifermin 50 mg group *vs* eight [19%] of 43 patients in the placebo group; all events except one were grade 1–2) and nausea (11 [28%] patients in the efruxifermin 28 mg group and 18 [42%] patients in the efruxifermin 50 mg group *vs* ten [23%] patients in the placebo group; all grade 1–2). Five patients (two in the 28 mg group and three in the 50 mg group) discontinued due to adverse events. Serious adverse events occurred in four patients in the 50 mg group; one was defined as drug related (ulcerative esophagitis in a participant with a history of gastro-oesophageal reflux disease). No deaths occurred.

Interpretation
Efruxifermin improved liver fibrosis and resolved NASH over 24 weeks in patients with F2 or F3 fibrosis, with acceptable tolerability, supporting further assessment in phase 3 trials.

ΕΜΜΑΝΟΥΗΛ ΚΟΥΛΛΙΑΣ

ΕΠΙΚΟΥΡΙΚΟΣ ΠΑΘΟΛΟΓΟΣ

Β’ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

ΓΝΑ ΙΠΠΟΚΡΑΤΕΙΟ

ΣΧΟΛΙΟ

Το Efruxifermin αποτελεί άλλη μία δραστική ουσία, στην προκειμένη περίπτωση έναν αγωνιστή του αυξητικού παράγοντα 21 των ινοβλαστών (FGF21), υποψήφια για την αντιμετώπιση ασθενών με μη αλκοολική στεατοηπατίτιδα και ίνωση (χωρίς κίρρωση). Ισχυρό σημείο της μελέτης αποτελεί η ένταξη ασθενών με στάδιο ίνωσης F2 και F3, ωστόσο, παρά τη στατιστική σημαντικότητα των ευρημάτων, η διενέργεια ευρύτερων και μεγαλύτερης διάρκειας κλινικών μελετών είναι αναγκαία για την πιστοποίηση παρουσίας ενδεχόμενου οφέλους όσον αφορά στην ίνωση και στη φλεγμονή στο ήπαρ, αλλά και στη διακρίβωση του πώς αυτό μεταφράζεται, σε βάθος χρόνου, σε κλινικό όφελος για τους ασθενείς.
Και σε αυτή την κλινική μελέτη ασθενών με NASH, η θετική ανταπόκριση στη χορήγηση του φαρμάκου δεν αφορούσε στην πλειοψηφία των ασθενών, επιβεβαιώνοντας ότι απέχουμε αρκετά από την ανεύρεση συνολικά αποτελεσματικής θεραπείας.

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