Eindrapportage ‘Short-term safety and efficacy of ketohexokinase inhibition in patients with hereditary fructose intolerance’ NL83631.068.22/ METC23-006

Name of Sponsor/Company: Institute of Nutrition and Translation Research in Metabolism (NUTRIM), Maastricht University	**Individual Study Table Referring to Part of the Dossier** N.A.	
Name of Finished Product: PF-06835919		
Name of Active Ingredient: PF-06835919		

Title of Study:
Short-term safety and efficacy of ketohexokinase inhibition in patients with hereditary fructose intolerance

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Publication (reference):
Results are not yet published.

Studied period (years): June 2023-November 2023	**Phase of development:** Phase IIa

Objectives:

To assess the effects of short-term treatment with PF-06835919 on intestinal, hepatic and renal fructose tolerance, and intrahepatic lipid content in patients with hereditary fructose tolerance.

Methodology:

In this single-arm, open label pilot study 3 patients with hereditary fructose intolerance (HFI) were treated for 8 days with PF-06835919 (300 mg, once daily). Two days after the start of the study medication, patients were exposed to a stepwise increase in oral fructose (2.5, 5.0 and 7.5 grams) to monitor intestinal, renal and hepatic tolerability. To exclude effects elicited by natural aversion against sweet taste HFI patients were also exposed to oral glucose tests (matched for sweetness to oral fructose: 5.3, 10.5 and 15.8 grams). Each block of oral tests always started with glucose and followed by fructose a day later, meaning that the first fructose challenge was performed after 4 doses of PF-06835919.

During each test the for up to 2 hours after consuming the fructose/glucose drink abdominal complaints were monitored, blood glucose and serum phosphate were measured, and fasting urine and post-test urine samples were collected for measurements of fructose, glucose, phosphate and pH.

Five healthy participants were included as a control, without PF-06835919 treatment. In these participants, the normal response to a 7.5 g oral fructose load was measured as reference values.

Number of patients (planned and analysed):
Planned: 8 (3 HFI, 5 controls)
Analyzed: 8

Diagnosis and main criteria for inclusion:
Inclusion criteria:

- Participants are able to provide signed and dated written informed consent prior to any study specific procedures
- Use of effective contraception (only applicable to premenopausal women; a pregnancy test will be performed in these women at baseline)
- Aged ≥ 18 years

Exclusion criteria:

- Diabetes mellitus
- Pregnancy
- Patients with congestive heart failure and/or severe renal and or liver insufficiency
- Uncontrolled hypertension
- Previous enrolment in a clinical study with an investigational product during the last 3 months or as judged by the investigator which would possibly hamper our study results
- Use of drugs that inhibit organic anion transporting polypeptide B1 (OATPB1) transporters (e.g. rifampicin, gemfibrozil, ciclosporine, erythromcyin and clarithromycin)*
- Treatment with irinotecan*
- Any contra-indications for MRI scanning*
- Subjects who do not want to be informed about unexpected medical findings

* Exclusion criterion for HFI patients only.

Test product, dose and mode of administration, batch number:
PF-06835919 (100 mg/tablet), 300 mg (3 tablets) per day, once a day in the morning, oral tablets
22-BU-00333

Duration of treatment:
8 days

Reference therapy, dose and mode of administration, batch number:
n/a

Criteria for evaluation:
Compliance was checked by counting the returned tablets and urinary fructose excretion, and daily checked by history taking. Participants were asked to maintain their habitual fructose restricted diet and regular physical activity pattern.

Statistical methods:
Results are presented as individual data. Graphs were created with GraphPad Prism.

Summary - Conclusions

Compliance:
Tablet counting and analysis of urinary fructose excretion indicated excellent compliance.
Urinary fructose excretion showed a dose-dependent increase.

Safety Results:
No adverse events were reported or observed based on the blood and urine safety analyses, done before the start of every fructose/glucose test. There were no reported (side-)effects during PF-06835919 treatment. No serious adverse events were reported related to the treatment with PF-06835919

Efficacy
None of the HFI patients reported any unwanted symptomatic effects after the subsequent challenge with increasing and graded doses of oral fructose. We observed inter-individual variation in serum phosphate and blood glucose response, ranging from a decrease in patient A to perfect tolerability towards even the highest dose of fructose in patient C.
In all three patients with HFI we observed a dose-dependent increase in fructosuria, upon PF-06835919-treatment after the fructose challenges.

We conclude that administration of PF-06835919 effectively suppresses hepatic fructose phosphorylation in overweight participants with MASLD, and thus offers a promising pharmacological profile for HFI as a possible add-on or replacement for the current standard of care. We contend that the outcome of this study warrants further exploration of the potential of pharmacological KHK inhibition with longer follow-up and clinically relevant endpoints in adults affected by HFI.

Date of report
06/11/24