Plain Language Summary

Safety, tolerability, pharmacokinetics, and pharmacodynamics of single ascending and multiple doses of nizubaglustat in healthy adults

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Plain Language Summary: The safety, tolerability, pharmacokinetics, and pharmacodynamics of single ascending and multiple doses of nizubaglustat in healthy adults.

What was this study about? This study was the first time a new medicine called nizubaglustat was given to humans. Nizubaglustat is being developed to treat neurological problems in people with certain genetic conditions called gangliosidoses (both primary and secondary forms, like Niemann-Pick type C). These conditions involve the buildup of specific fatty substances in the body, especially in the brain. The main goals of this study were to see if nizubaglustat was safe and well-tolerated, how the body handled the medicine (pharmacokinetics), and how it affected certain biological markers (pharmacodynamics).

Who participated in the study? The study included healthy adult volunteers, aged 18 to 55 years. In the first part, 23 subjects received single doses, and in the second part, 12 subjects received multiple doses.

What was tested? The researchers tested nizubaglustat. This medicine is designed to work in two ways by blocking two enzymes:

1. It blocks an enzyme called ceramide glucosyltransferase (GCS), which helps make fatty substances that can build up in these diseases.
2. It also blocks another enzyme called non-lysosomal neutral glucosylceramidase (NLGase), which is involved in breaking down these fatty substances outside of the cell's recycling centers (lysosomes). This dual action is intended to reduce the harmful buildup of these fats, particularly in the brain.

How was the study done? This was a "first-in-human," randomized, double-blind, placebo-controlled study. This means:

- **First-in-human:** It was the initial time the drug was given to people.
- **Randomized:** Participants were randomly assigned to receive either nizubaglustat or a placebo (a dummy pill).
- **Double-blind:** Neither the participants nor the study staff knew who was receiving the actual medicine.
- **Placebo-controlled:** One group received nizubaglustat, and another received the placebo for comparison. The study had two parts:
- **Part 1:** Participants received a single dose of nizubaglustat (1 mg, 3 mg, or 9 mg).
- **Part 2:** Participants received multiple doses of 9 mg nizubaglustat once daily for 14 days. Researchers collected blood, urine, and some cerebrospinal fluid (fluid around the brain and spinal cord) samples to measure drug levels and biological markers.

What were the main findings? The study found that:

- **Safety and Tolerability:** Nizubaglustat was safe and well-tolerated at all doses tested. Importantly, unlike some other similar medicines, it did not cause diarrhea, decreased appetite, or weight loss. The only drug-related side effects were mild skin issues, which are consistent with how the medicine works.

- **How the Body Handled the Medicine (Pharmacokinetics):** Nizubaglustat was quickly absorbed into the body, and the amount in the bloodstream increased predictably with higher doses. When given daily, it reached a steady level in the body within about three days, with minimal buildup. About 15% of the medicine was removed from the body through urine.
- **How the Medicine Affected Biological Markers (Pharmacodynamics):**
    - In the blood, levels of certain fatty substances (glucosylceramide, lactosylceramide, and GM3 ganglioside) significantly decreased, indicating that nizubaglustat was effectively blocking the GCS enzyme. These levels dropped by up to 70% after 10 days of daily dosing.
    - In the cerebrospinal fluid, levels of glucosylceramide increased. This indicates that nizubaglustat was also effectively blocking the NLGase enzyme in the brain, which is important for its potential to treat neurological symptoms.

What do these findings mean? These results show that nizubaglustat is safe and well-tolerated in healthy adults, and it effectively targets the intended biological pathways. The findings support giving the medicine once a day, and suggest that it can reach the brain, which is crucial for treating the neurological problems. This study provides the foundation for further development of nizubaglustat as a potential treatment for patients with NPC and similar disease states.