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Diabetes mellitus (DM), a disorder of glucose homeostasis, is the third major risk factor for chronic diseases. But no satisfactory drug therapy for disease management exists. Diabetes drug discovery and development is a major challenge for the pharmaceutical industry. We are in a position to recommend to the industry the use of the SGLT2 inhibitor phlorizin for the treatment of type 2 diabetes. We found phlorizin to have a high safety margin. It is a natural product that does not have major metabolic liabilities. In fact, it has been used as a food supplement for many years. The isolation and identification of phlorizin from plants has also been described in several papers. We worked with Michael Czernik of the Mayo Clinic Medical School. He and his colleagues isolated phlorizin from apple and sweet potato and identified it as a metabolite of chlorogenic acid (CGA) biosynthesis. The discovery that metformin inhibits phlorizin uptake into epithelial cells is novel. But it did not lead us to new avenues of investigation. We are currently trying to discover novel SGLT2 inhibitors. Supplementary materials Our company made several compounds that inhibited the SGLT2 transporter by different mechanisms, including in situ phlorizin derivatives. Lead compound, TAK-603, used an AMP analogue as a scaffold, with the aim of protecting it from metabolism and increasing oral bioavailability. TAK-603 has a good balance of potency and safety margin. Our findings showed that TAK-603 can protect the AMP analogue in the gut lumen and also have a degree of SGLT2 selectivity. The clinical safety profile of TAK-603 was comparable to that of phlorizin, a known SGLT2 inhibitor. This made TAK-603 a candidate for additional preclinical studies to evaluate its therapeutic potential. We think that TAK-603 is a promising orally active antidiabetic agent for the management of type 2 diabetes and related chronic complications. Previous studies with TAK-603 confirmed that the oral delivery route is feasible in animal models. This report describes the development and characterization of a multiple-dose, oral formulation, the pharmacokinetics, metabolism, and excretion of TAK-603, and the safety profile in cynomolgus monkeys, rats, and dogs.

TAK-603 was a safe and well-tolerated SGL 3e33713323

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