**Elsiglutide in the primary prevention of chemotherapy (CT)-induced diarrhea in patients with colorectal cancer (CRC) receiving 5-fluorouracil (5-FU)-based CT: A multinational, randomized, double-blind, placebo-controlled study.**

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**Background:** Diarrhea is a burdensome toxicity of 5-FU-based regimens and may lead to CT dose intensity reduction. We investigated the efficacy of 3 subcutaneous (s.c.) doses of elsiglutide (a GLP-2 analog) vs. placebo and vs. each other, in the primary prevention of CT induced diarrhea in patients (pts) with CRC receiving FOLFOX or FOLFIRI. **Methods:** Pts were randomized equally to receive placebo or elsiglutide 10, 20, or 40 mg s.c. on days (d)1–4 of the first 2 CT cycles and were followed up in cycle 3 for safety only. Stratification factors were CT regimen and country. Primary endpoint was the proportion of pts with diarrhea of CTC grade ≥2 in cycle 1. Changes in plasma levels of citrulline, a marker of intestinal mass, from baseline to d5 and d14 of each cycle were analyzed. With 480 pts randomized, the study had 85% power to detect a 15% difference vs. placebo for each dose at an alpha level of 0.1, assuming a 20% frequency of diarrhea CTC grade ≥2 in the placebo arm. **Results:** Treatment groups were comparable for the 484 pts (142 receiving FOLFIRI) who were randomized to receive placebo (n = 123), elsiglutide 10 mg (n = 120), 20 mg (n = 121), or 40 mg (n = 120), respectively. The proportion of pts with diarrhea CTC grade ≥2 was higher with placebo (10%) than with elsiglutide 10 mg (3%), 20 mg (5%) and 40 mg (6%); differences were not statistically significant. A similar pattern was observed in cycle 2. Differences in diarrhea frequency between placebo and elsiglutide groups were pronounced in the FOLFIRI subgroup (cycle 1: 18% with placebo, 6% with 10 mg and 20 mg; 3% with 40 mg elsiglutide). Reduction of citrulline levels was smaller with elsiglutide compared with placebo. The safety profile of all elsiglutide doses was acceptable with few related injection site reactions, mostly at the highest dose. **Conclusions:** Although a lower frequency of diarrhea CTC grade ≥2 was observed with elsiglutide, this difference was not statistically significant in pts receiving FOLFOX or FOLFIRI for CRC. Interpretation must consider the unexpectedly low reported frequency of diarrhea of grade ≥2, particularly with FOLFOX regimens.