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Albiglutide for the treatment of type 2 diabetes mellitus: An integrated safety analysis of the HARMONY phase 3 trials

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ABSTRACT

Aims: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) stimulate the incretin system and lower glycaemic parameters in type 2 diabetes mellitus (T2DM). This analysis of clinical studies of up to 3 years evaluated the safety of albiglutide, a GLP-1 RA, in people with T2DM.
Methods: Integrated safety analysis included seven phase-3 T2DM studies of albiglutide compared with placebo and/or active comparators (a dipeptidyl peptidase-4 inhibitor, GLP-1 RA, insulin, sulphonylurea, and thiazolidinedione).
Results: Studies of 32 months (HARMONY 7), 1 year (HARMONY 6), and 3 years (HARMONY 1–5), reported similar rates of adverse events (AEs) (84.8%, 82.3%), and serious AEs (13.1%, 12.9%) between albiglutide and all comparators, respectively. AEs that did not differ between the groups included symptomatic or severe hypoglycaemia as well as nausea (12.0%, 11.3%) and vomiting (5.3%, 4.7%) for albiglutide and all comparators, respectively. According to the Medical Dictionary for Regulatory Activities preferred terms, only diarrhoea (13.7%, 9.9%), injection-site reaction (9.0%, 2.0%), and peripheral oedema (4.5%, 6.8%) had at least 2% difference between the albiglutide and all-comparator groups. In a similar integrated analysis, pancreatitis occurred more often with albiglutide (0.3%, 0.1%). Renal and cardiac function did not differ between the two groups.
Conclusions: In an integrated analysis of seven phase 3 clinical trials, albiglutide-treated patients experienced frequencies of AEs (including cardiovascular and renal) similar to the all-comparators group treated with other T2DM medications or placebo. Albiglutide treatment was associated with higher rates of diarrhoea and injection-site reactions, but not increased nausea and vomiting, versus all comparators.

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1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been developed as novel glucose-lowering therapies in type 2 diabetes mellitus (T2DM) [1]. Albiglutide is a recombinant fusion protein consisting of two linked copies of a modified 30-amino acid sequence of human GLP-1 (fragment 7–36) genetically fused in series to human albumin [2–4]. A single amino acid substitution at position 8 of the GLP-1 sequence (ala → gly) confers resistance to proteolysis by dipeptidyl peptidase-4 (DPP-4) [2]. Fusion with albumin and resistance to DPP-4 degradation give albiglutide a half-life of approximately 5 days, allowing for once-weekly dosing [3,5,6]. Albiglutide has been shown to reduce glycaemic parameters (eg, HbA1c, postprandial glucose excursions, and fasting plasma glucose [FPG]) in association with enhancement of glucose-dependent insulin secretion and slowing of gastric emptying [2–5,7].

The HARMONY phase 3 program included eight randomised, double-blind or open-label, placebo- and/or active-controlled trials (Table 1) that evaluated the efficacy and safety of albiglutide in patients with T2DM who were inadequately controlled on their current regimen of diet and exercise, oral antidiabetes drugs (OADs), or basal insulin. The length of the trials ranged from 32 weeks to 3 years and included more than 4800 patients (Table 1). The results of each trial at the primary endpoint and, for 5 of the studies, at a time point of 3 years have been reported separately [8–17]. After 3 years' treatment, albiglutide was associated with reductions in HbA1c and FPG and with modest weight loss. Given the size and duration of exposure, the program offers a unique opportunity to evaluate the long-term safety of albiglutide. We present an integrated analysis of the safety of albiglutide in the HARMONY phase 3 program, including data out to 3 years.

2. Methods

2.1. Study design

Seven studies in the HARMONY program (Table 1) were integrated for safety analysis. Five of the phase 3 studies had preplanned continuation of randomised treatment out to 3 years. The integrated studies included patients treated with albiglutide as monotherapy, in combination with one to three OADs, or with insulin (basal). The pooled "all-comparators" group in the integrated analysis includes a range of active comparators (metformin, sulphonylurea [SU], thiazolidinedione [TZD], DPP-4 inhibitor, insulin [basal and lispro], or GLP-1 RA [liraglutide]) as well as placebo comparator. HARMONY 8 [15], which enrolled patients with mild, moderate, and severe renal impairment, was excluded from this integrated analysis due to the unique safety characteristics of such patients, although results of the HARMONY 8 study [15] were included in separate integrated analyses of adjudicated pancreatitis and cardiovascular events, discussed later in this article.

Albiglutide had a starting dose of 30 mg weekly in all the phase 3 studies. In most of these studies, albiglutide could be uptitrated to 50 mg, based on prespecified glycaemic criteria, or was uptitrated by design (Table 1). The HARMONY program also permitted the addition of hyperglycaemia rescue medication for participants who did not meet glycaemic goals, in line with US Food and Drug Administration (FDA) guideline recommendations [18]. These studies were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki, and all participants provided written informed consent.

2.2. Key inclusion and exclusion criteria

Detailed inclusion and exclusion criteria for the individual trials have been reported elsewhere [8–15]. These studies included men or women ≥18 years old, with HbA1c 7%–10% (53–86 mmol/mol) (or HbA1c 7%–10.5% [53–91.5 mmol/mol] for HARMONY 6) with T2DM that was inadequately controlled with diet and exercise, OADs, or basal insulin. Exclusion criteria included a history of cancer (except non-melanoma skin cancers) not in remission for 3 years, treated diabetic gastroparesis, current symptomatic biliary disease, a history of pancreatitis, previous significant gastrointestinal (GI) surgery, or recent clinically significant cardiovascular disease.

2.3. Statistical analysis

The safety population was defined as patients who received at least one dose of study medication. Baseline demographics and on-therapy adverse events (AEs) were tabulated using descriptive statistics. Safety data were integrated and analysed irrespective of albiglutide dose (30 mg or 50 mg). Due to the long half-life of albiglutide, on-therapy AEs included events that occurred from the first dose of study medication to within 56 days after the last dose of study medication.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 14.0), summarised by MedDRA system organ class and preferred term. Select AEs of interest were summarised using MedDRA query searches. Hypoglycaemia AEs were characterised using 2013 American Diabetes Association (ADA) criteria [19] and are summarised prior to the addition of hyperglycaemia rescue medication by individual study, due to the differing background antidiabetic medications and associated risks of hypoglycaemia. Cardiovascular and pancreatitis events were adjudicated by respective independent adjudication committees described elsewhere in detail [14,20,21].

3. Results

3.1. Study participants and treatment exposure

The integrated safety population comprised 4400 T2DM patients who received at least one dose of study medication (Table 2). Of the participants in these trials, 5 of which lasted for 3 years (Table 1), 69.3% treated with albiglutide and 67.5% treated with a comparator completed their respective study treatment as planned. The most common reasons for