This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

Synopsis

Identifier: RM2006/00207/00 **Study Number:** SB-767905/011, SB-767905/012, SB-767905/014, SB-767905/008, ABD101684

Title: Population Pharmacokinetic Analysis of Alvimopan and its Metabolite in Patients with Opioid Bowel Dysfunction and Healthy Volunteers

Phase of development: II/III

Objectives:

- To characterize the population pharmacokinetics of alvimopan and its amide hydrolysis metabolite and describe the covariates which may explain variability in pharmacokinetics

Endpoints:

- Plasma concentrations of alvimopan and metabolite

Methodology:

Plasma concentration-time data, demographic data, and dosing data were combined from studies in healthy subjects conducted by Adolor (Studies 14CL116, 14CL117, 14CL118, 14CL119, 14CL123, 14CL124, 28CL201, 14CL125, 14CL127) and by GSK (Study SB-767905/016), from Japanese healthy subjects (SB-767905/018 and 019), and from subjects with opioid bowel dysfunction (OBD) with either noncancer pain (SB-767905/011, SB-767905/012 SB-767905/014) or cancer pain (SB-767905/008).

Data were assembled from each of the clinical studies in which subjects received oral doses of alvimopan as one or more capsules and a single comprehensive data set was formatted for analysis. Data analysis was performed using the nonlinear mixed effects modeling program NONMEM system (Version 5, Globomax Corporation, Baltimore, MD). Estimates for population mean parameters (typical values), standard errors of parameters, coefficient of variation (%), interindividual variability, and residual variability were obtained.

An appropriate structural pharmacokinetic model was developed previously, based on review of the known and plausible pharmacology of alvimopan and its metabolite. The covariate model was then developed, based on univariate analysis, followed by backward elimination.

The following covariates were pre-specified for inclusion in the analysis: Age, Weight, Gender, Food (High fat, low fat, or mixed), Dose, Race: (Caucasian; African-American; Hispanic; Japanese, Other), and creatinine clearance (determined using the Cockcroft-Gault nomogram). In addition, subject type was pre-specified for inclusion in the

analysis as: Inflammatory Bowel Disease (Study 14CL125); OBD (cancer and noncancer combined), and cancer OBD (cancer only) (SB-767905/008).

Assay: Plasma assays were performed with a single validated liquid chromatographic/ mass spectroscopy (MS)/MS technique by three different vendors, with several different lower limits of quantification (LLQ) (0.05, 0.1, or 0.25 ng/mL).

Concomitant medications included: Antibiotics targeting gut microflora, drugs that inhibit the organic anion transporter pump (OATP inhibitors), drugs that inhibit P-glycoprotein (PGP inhibitors), drugs that are potent PGP inhibitors, and drugs that block gastric acid (Histamine-2 blockers or proton pump inhibitors).

Summary:

The alvimopan plasma concentration-time data were described well using a two-compartment model with first order absorption and a lag time. The typical values of CL/F, Vss/F, and intercompartmental CL/F were 231 mL/min, 1424 L, and 64.0 mL/min, respectively. The magnitudes of inter-individual variability in CL/F, V/F, intercompartmental CL/F were moderate to large (55%, 69%, and 89%, respectively). The typical values of ka and lag time in the fasted state were 0.519 min^{-1} and 0.411 hr, respectively. The bioavailability[1] was 11% lower, the rate of absorption was slower (0.332 min^{-1}) and the lag time was longer (0.892 hr) when alvimopan was administered in the fed state. The bioavailability was 1.96 times higher in Japanese subjects than in non-Japanese subjects, 1.49 times higher in IBD subjects than in all other subjects, and 1.49 times higher in subjects receiving OATP inhibitors than in those not receiving OATP inhibitors. The bioavailability was 19% lower in those subjects receiving a 24 mg dose than in those subjects receiving lower doses. The bioavailability was also slightly related to renal function, with a 24% higher bioavailability in those with low renal function and 24% lower bioavailability in those with high renal function, when compared to the median creatinine clearance. The CL/F was 22% lower in Hispanics than in all other races; and 19% higher in smokers than in nonsmokers or those with an unknown smoking status.

The metabolite plasma concentration-time data were described well using a one compartment model with a catenary chain (n=2) describing absorption, where mean transit time (MTT=number of catenary chains/ka) describes the rate of absorption. The typical values of CL/F and Vss/F were 42.0 mL/min and 1640 L, respectively. Bioavailability was 9% lower in the fed state. The MTT values were 13.7 and 22.7 hrs in the fasted and fed state, respectively. The magnitudes of inter-individual variability in CL/F, V/F, and MTT were large or very large (96%, 115%, and 341%, respectively). The V/F was 10.5 times higher in Hispanic subjects than in nonhispanic subjects. The

[1] Because only oral dosing of alvimopan was studied, it is impossible to differentiate whether this effect is a true effect on bioavailability or if the effect is due to parallel changes in the CL, V and intercompartmental CL

bioavailability was 1.7 times higher in cancer subjects than in noncancer subjects or healthy subjects; 60% lower in IBD subjects than in nonIBD subjects; 26% lower in black subjects than in nonblack subjects; 24% higher in patients receiving PGP inhibitors than in those not receiving PGP inhibitors; and 48% lower in smokers than in nonsmokers or those with unknown smoking status. The bioavailability was 27% lower and 57% higher for the 2.5^{th} and 97.5^{th} percentile of CrCL (46 and 175 mL/min, respectively), when compared to the median CrCL (100 mL/min).

Conclusions:

- Alvimopan and metabolite pharmacokinetics did not differ significantly between healthy subjects and OBD subjects, on average, although variability estimates were different for OBD subjects and for healthy subjects. Variability in pharmacokinetics was not explained by age or gender.
- Alvimopan pharmacokinetics did not differ between cancer and noncancer OBD subjects, but metabolite concentrations are higher in cancer OBD subjects (1.7x) than in noncancer OBD subjects or healthy subjects. This effect is unlikely to be clinically relevant.
- Race influenced the pharmacokinetics of alvimopan and metabolite. Japanese subjects had an approximately 2-fold increase in plasma concentrations of alvimopan, but no change in metabolite pharmacokinetics. Hispanic subjects had a lower CL/F of alvimopan resulting in higher concentrations of alvimopan later in the profile, but not at the time of Cmax and a lower F of metabolite resulting in slightly lower concentrations of metabolite throughout a dosing interval. No dosage adjustments are considered necessary. However, the possibility of increases in AEs (e.g., diarrhea, gastrointestinal pain, and abdominal cramping) in Japanese or Hispanic OBD subjects due to higher alvimopan concentrations cannot be ruled out
- Concomitant administration of OATP inhibitors (e.g., atorvastatin, gemfibrozil) was associated with a 1.5 times higher plasma concentrations of alvimopan. No dosage adjustments are considered necessary. However, the possibility of increases in AEs (e.g., diarrhea, gastrointestinal pain, and abdominal cramping) in these OBD subjects due to higher alvimopan concentrations cannot be ruled out.
- IBD subjects had a 1.5-fold increase in plasma concentrations of alvimopan and 60% reduction in metabolite concentrations. These effects counterbalance each other and are not likely to be clinically relevant.
- Although not clinically relevant, small amounts of variability in alvimopan and metabolite pharmacokinetics were explained by renal function and smoking, while small amounts of variability in metabolite pharmacokinetics were also explained by concomitant administration of PGP inhibitors and black race.

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