Name of Sponsor/Company: Astellas Pharma Europe B. V.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP9831		

Title of Study: A Phase II, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 12-Week Treatment, Adaptive Proof-of-Principle Study of Twice Daily Oral Dosing of a Novel PDE4 Inhibitor (ASP9831) in Subjects with Non-Alcoholic Steatohepatitis (NASH)

Responsible Officer/Investigators:

Responsible Officer:
[redacted]
The Netherlands

Coordinating Investigator:
[redacted]
France

Study Centers: Study part 1 was conducted at 3 study sites (2 in France and 1 in the United Kingdom).

Study part 2 was conducted at 22 sites in 7 countries in Europe (Belgium, Czech Republic, France, Germany, Romania, Switzerland and the United Kingdom). Investigator information and affiliation are provided in Appendix 13.1.4.

Publication (reference): Results of this study have not been published at the time of report preparation.

Study Period: March 2008 to Q4 2010

Phase of Development: Phase 2

Date of first informed consent: April 3, 2008

Date of last evaluation: October 8, 2010

Objectives:

Objective Part 1

- To explore exposure to ASP9831 in patients with NASH and to compare the data with healthy volunteer data.

Primary Objective Part 2

- To study the effect of a 12-week treatment with 2 dose levels of ASP9831 compared to placebo on liver injury by assessing serum levels of alanine aminotransferase (ALT) in subjects with NASH.

Secondary Objectives Part 2

- To study the safety of 2 dose levels of ASP9831 compared to placebo in subjects with NASH.
- To perform an exploratory analysis of
  - the effect of ASP9831 on hepatic steatosis
  - the effect of ASP9831 on liver inflammation and vascular damage
  - the effect of ASP9831 on other liver injury markers
  - the effect of ASP9831 on liver fibrosis
  - the effect of ASP9831 on insulin resistance
  - the effect of ASP9831 on clinical symptoms
  - the pharmacokinetics and the pharmacokinetic/pharmacodynamic relationships of ASP9831 in the study population

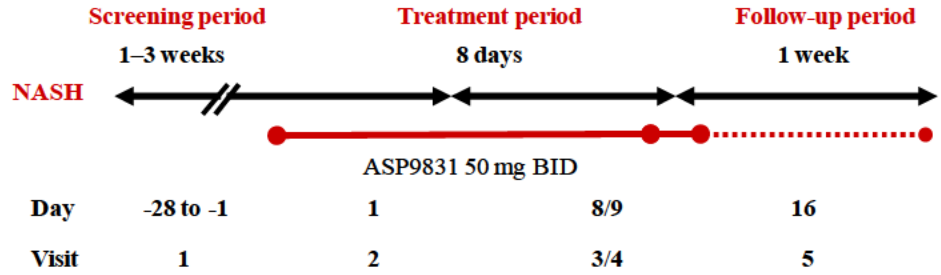
Methodology: This was a proof-of-principle study consisting of 2 parts:

1. Part 1 was an open-label sub-study that investigated exposure levels of ASP9831 in a cohort of patients with confirmed NASH.
2. Part 2 was the main study and was a randomized, double-blind, parallel-group, placebo-controlled study using biomarkers as outcome measures.

Study patients with a diagnosis of NASH were selected from outpatients with elevated serum ALT levels who were willing to participate in the study and provide written informed consent, who had a liver biopsy performed within 1 year prior to the first dose (part 1) or randomization (part 2).

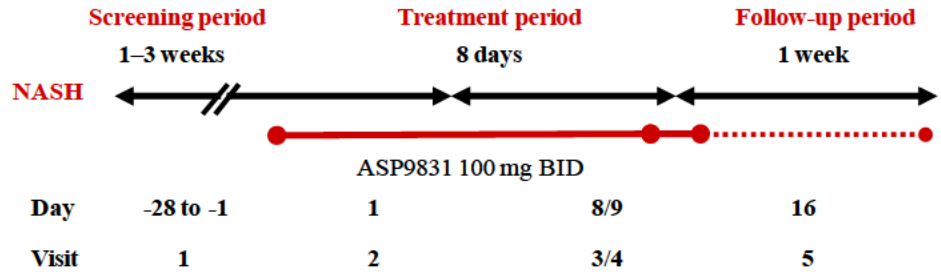
Part 1 also consisted of 2 parts (part 1a and part 1b). Part 1a was designed to evaluate the exposure to ASP9831 and the safety and tolerability of ASP9831 in 6 patients with NASH fibrosis stage F3 who were treated with ASP9831 50 mg twice daily (BID) for 8 days (day 1 through day 8). The treatment period was followed by a 1-week safety follow-up period without study medication [Figure 1]. Determination of ASP9831 exposure was based on serial blood samples obtained over a 24-hour postdose period on day 8. Patients were to return in the morning of day 9 for collection of the final blood sample (24 hours postdose). Safety assessments consisted of reporting all adverse events (AEs) with onset any time after provision of informed consent until the last study contact, recording of vital signs and any concomitant medication, evaluation of safety laboratory assays (biochemistry, hematology and urinalysis) performed at each visit and a 12-lead electrocardiogram (ECG) performed on day 1 and day 8.

Figure 1 Flow Chart Study Part 1a



Based on the pharmacokinetic exposure data analysis of part 1a, it was to be decided if part 1b could be performed as planned or not. In part 1b, the same 6 patients or an additional 6 patients with NASH fibrosis stage F0 to F3 were to be enrolled and treated with ASP9831 100 mg BID for 8 days. The assessments and schedule in part 1b were the same as part 1a [Figure 2].

Figure 2 Flow Chart Study Part 1b



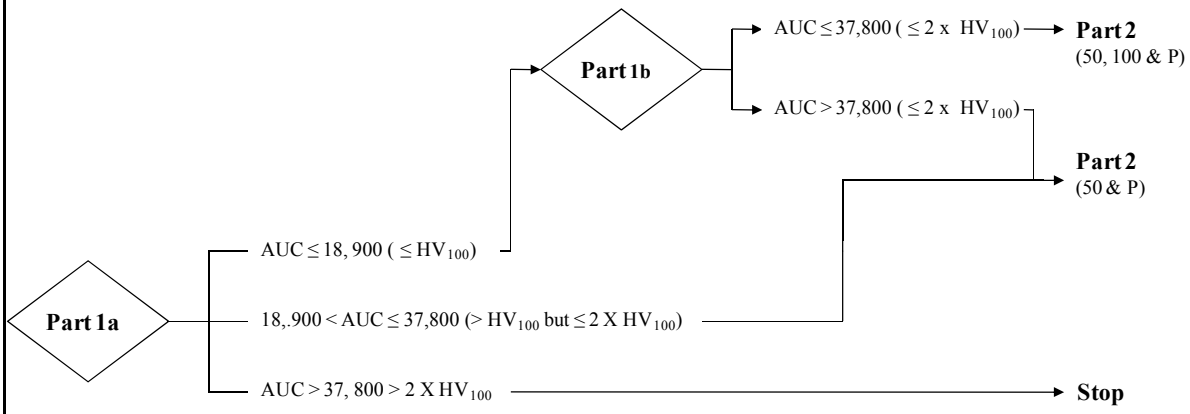
In view of the absence of clinical data with ASP9831 in patients with NASH, the design of study parts 1a and 1b included an early analysis of the exposure to ASP9831. Study part 2 could not start until the results from the exposure analysis of part 1 were available. Exposure data from a phase 1 multiple dose study in healthy volunteers were used to compose a decision algorithm with respect to ASP9831 exposure in the current study. Results obtained during part 1 were to be evaluated in comparison to the observed exposure data from the phase 1 study. In the prior study, the mean area under the concentration time curve from the time of dosing until 24 hours postdose (AUC_{24h}) at steady state across all volunteers receiving multiple doses of 100 mg ASP9831 BID was 18918 ng*hr/mL. The rounded figure of 18900 ng*hr/mL was taken as the reference value in the algorithm employed in the decision process subsequent to study parts 1a and 1b. *Continued→*

The algorithm ensured that the predicted mean maximum exposure to ASP9831 in part 2 would not exceed 37800 ng*hr/mL of total ASP9831 (i.e., twice the mean AUC following 100 mg BID in healthy volunteers) which corresponded to 113 ng*hr/mL of unbound ASP9831 (human plasma protein binding of 99.7%) [Study 9831-ME-0021].

Safety data from patients in part 1a and 1b were also to be reviewed but were not formally included in the algorithm due to the small number of patients studied and the possible variability in the data making it difficult to compare quantitatively to the safety data in healthy volunteers. Unless there were obvious and large differences in the type and severity of AEs, these would not affect the choice of doses in part 2. The decision for the dose selection in part 2 was to be made by the sponsor and the sponsor was then to inform the Data Safety Monitoring Board (DSMB) of the decision. The DSMB was installed to monitor overall study safety and to adjudicate suspected cases of colitis if applicable.

When part 1a and part 1b were completed and the ASP9831 exposure determined in the target population, study part 2 could be initiated with 1 of 2 treatment regimens over a 12-week treatment period [Figure 3]: 3 treatment arms consisting of ASP9831 50 mg BID, ASP9831 100 mg BID and placebo BID or 2 treatment arms consisting of ASP9831 50 mg BID and placebo BID. After NASH diagnosis confirmation and determination of eligibility, 93 patients with NASH fibrosis stage F0 to F3 were then to be enrolled in order to have at least 75 patients who completed part 2 per protocol. Patients were to be stratified by study site and randomized by balanced ratio to 1 of 3 or 1 of 2 treatment arms, depending on the outcome of the exposure data analyses of part 1 of the study [Figure 3].

Figure 3 Algorithm Linking Study Parts 1a, 1b and 2



Duration of treatment in both part 1a and part 1b was 8 days.

HV_{100}: healthy volunteer study (9831-CL-0001) with ASP9831 100 mg BID for 8 days

50, 100 & P: 3 treatment arms consisting of ASP9831 50 mg BID, 100 mg BID and placebo BID for 12 weeks

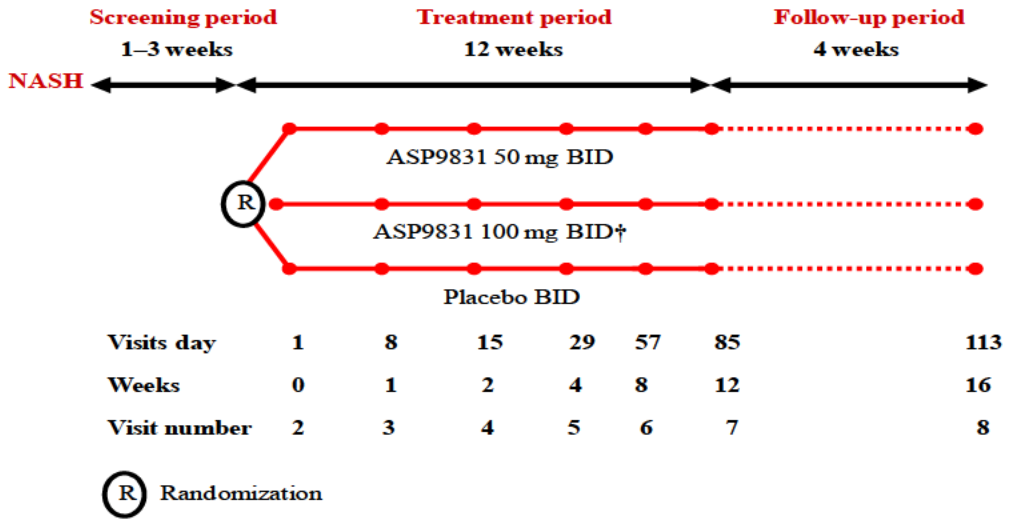
50 & P: 2 treatment arms consisting of ASP9831 50 mg BID and placebo BID for 12 weeks

Based on the outcome of part 1, the 3 treatment arms scenario was subsequently evaluated in part 2 [Figure 4]:

- ASP9831 50 mg BID
- ASP9831 100 mg BID
- placebo BID

each administered for 12 weeks followed by a 4-week safety follow-up period (i.e., without study medication).

Figure 4 Flow Chart Study Part 2



†Based on the early pharmacokinetics analysis in part 1 and the decision algorithm, the doses for part 2 were selected.

Part 2 was designed to evaluate the effect of ASP9831 on steatosis, liver inflammation and vascular damage, liver injury and fibrosis through evaluation of biomarkers and to assess the safety of ASP9831 in this patient population. The primary proof-of-principle assessment was based on the percentage change in serum ALT levels at the end of 12 weeks of treatment compared with baseline ALT levels between patients treated with ASP9831 and placebo.

Fasting blood samples for biochemistry and hematology and urine for analysis were obtained at each site visit except visit 1. Population pharmacokinetic assessments were based on plasma levels of ASP9831 obtained in all patients at 1 or 2 visits on visit 4 (day 15), visit 5 (day 29), visit 6 (day 57) or visit 7 (day 85). Any time a pharmacokinetic assessment was scheduled, the patient was to be instructed to record the time of the last evening dose and to come to the clinic before breakfast. Four blood samples were to be obtained over a 12-hour period. Safety assessments consisted of reporting all AEs with onset any time after provision of informed consent until the last study contact, recording of vital signs and any concomitant medication at each visit and performance of a 12-lead ECG on visit 2 (day 1), visit 3 (day 8), visit 5 (day 29) and visit 7 (day 85).

Number of Patients (planned, enrolled and analyzed):

Planned: The protocol called for 12 patients to be included in part 1 and for 93 patients in total to be randomized in part 2.

Enrolled: 15 patients in total were enrolled in part 1: 8 in part 1a and 7 in part 1b; however, 1 patient was withdrawn from part 1a prior to receipt of study drug as result of noncompliance with an eligibility criterion [Figure 5]. Ninety-nine patients in total were enrolled in part 2: 30 in the placebo group, 35 in the ASP9831 50-mg group and 34 in the ASP9831 100-mg group.

Analyzed: The protocol defined 4 populations for analysis. For part 1, patients were identified for the analyses populations in a data review meeting (DRM) before database hard lock. For part 2, patients were identified for the analyses populations in a blinded data review meeting (BDRM) prior to database lock and unblinding. See Figure 5 for the summary of patient disposition and analyses sets.

Safety Analysis Set (SAF): The SAF consisted of patients who took at least 1 tablet of study medication as confirmed by returned medication: 14 patients in part 1 (7 in both part 1a and 1b); 96 patients in part 2 (30 in the placebo group and 33 in both the ASP9831 50-mg and 100-mg groups).

Analyses sets description continued→

Full Analysis Set (FAS): The FAS consisted of all patients who took at least 1 tablet of study medication and had at least 1 post-baseline value of ALT: 94 patients in part 2 (29 in the placebo group, 32 in the ASP9831 50-mg group and 33 in the ASP9831 100-mg group).

Per Protocol Set (PPS): The PPS was a subset of the FAS consisting of all patients who adhered sufficiently to the protocol: 82 patients in part 2 (25 in the placebo group, 29 in the ASP9831 50-mg group and 28 in the ASP9831 100-mg group).

Diagnosis and Main Criteria for Inclusion:

During the course of the study, eligibility criteria were amended in protocol amendment 1 (February 14, 2008), protocol amendment 2 (June 23, 2008), protocol amendment 3 (October 8, 2008) and protocol amendment 4 (June 11, 2009). Therefore, patients who participated in part 1a were enrolled under eligibility criteria effective under amendments 1 and 2. All patients who participated in part 1b were enrolled under eligibility criteria effective under amendment 3 or 4.

Male and female patients 18 years of age or above with a diagnosis of NASH and who signed written informed consent prior to screening were considered for participation in the study.

A patient in this category was eligible for enrollment in part 1 of the study if the following additional criteria were met:

- For part 1a: The patient had NASH, fibrosis stage F3 (zone 3 perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis) histologically confirmed by a liver biopsy performed within 1 year prior to the first dose.
- For part 1b: The patient had NASH, fibrosis stage F0 to F3 histologically confirmed by a liver biopsy performed within 1 year prior to enrollment.
- The patient had elevated serum ALT levels at screening below 300 U/L according to central laboratory analysis.
- The patient had elevated serum ALT levels on 2 occasions tested within 1 year prior to screening according to local laboratory normal ranges.

A patient in this category was eligible for enrollment in part 2 of the study if all of the following additional criteria were met:

- The patient had NASH, fibrosis stage F0 to F3, histologically confirmed by a liver biopsy performed within 1 year prior to randomization.
- The patient had elevated serum ALT levels at screening of at least 1.5 times the upper limit of normal (ULN) with a maximum of 300 U/L according to central laboratory analysis.
- The patient had serum ALT > 1.5 X ULN or > 60 IU/L (local laboratory) on 1 occasion in the previous 6 months and no documented normal value in the previous year.

The main criteria for exclusion of a patient from the study were the following (numbers between parentheses indicate the exclusion criteria numbers in the protocol):

- The patient was diagnosed with hepatic cirrhosis (1).
- The patient had other known cause of liver disease (autoimmune, viral, genetic, drug induced, alcoholic liver disease or storage disease) or drug-induced hepatotoxicity (4).
- The patient had an unstable metabolic condition (i.e., with weight change > 5% in the 6 months prior to screening and/or initiation and subsequent continuous use of antidiabetic drugs (including insulin sensitizing agents), antihypertensives and/or lipid lowering drugs within 4 months prior to screening (5).
- The patient had uncontrolled diabetes mellitus type 2 (i.e., hemoglobin A1C > 8.5%) (6).
- The patient had a positive history of tuberculosis or a positive purified protein derivative (PPD) skin test which was not explained by previous Bacillus Calmette-Guerin (BCG) vaccination (13).
- The patient had a history of excessive alcohol abuse within 5 years prior to screening or a current average alcohol intake of more than 20 g/day (2 units) for females or more than 30 g/day (3 units) for males (15).
- The patient had used drugs associated with steatohepatitis within 6 months prior to screening (corticosteroids, high dose estrogens, methotrexate, amiodarone, anti-HIV drugs, tamoxifen) (17).

Main exclusion criteria continued

- The patient used concomitant medications which are mainly metabolized by CYP2C8/9 and which have a narrow safety margin (warfarin, phenytoin, paclitaxel and tolbutamide) (20).

Test Product, Dose and Mode of Administration, Batch Numbers:

The test drug for this study was supplied as immediate-release tablets for oral administration. Tablets containing ASP9831 were provided in strengths of 5, 20 and 40 mg. ASP9831 is a yellow crystalline powder and is chemically 3-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-yl] propanoic acid. The molecular formula of ASP9831 is $C_{20}H_{23}N_3O_3$ and its molecular weight is 353.41 Daltons.

Tablets were manufactured by [redacted]. Study drug batches were released by Astellas Pharma Europe B.V., The Netherlands. Batch numbers [redacted] (5-mg tablet), [redacted] (20-mg tablet), [redacted] and [redacted] (40-mg tablet) were used in part 1 of the study. Batch numbers [redacted] and [redacted] (5-mg tablet), [redacted] (20 mg tablet); [redacted] and [redacted] (40-mg tablet) were used in part 2 of the study.

In part 1a of the study, patients were treated with open-label ASP9831 50 mg BID for 8 days. In part 1b of the study, patients were treated with open-label ASP9831 100-mg BID for 8 days. In part 2, patients were randomized into 1 of 3 treatment arms: ASP9831 50 mg BID, ASP9831 100 mg BID or placebo BID.

To compose the 50- and 100-mg dosages, all patients received 3 tablets for each dose and 6 tablets per day in total. The table below shows the tablet strengths for each dose group. The tablets were to be taken orally within 30 minutes after consumption of a meal, with a minimum of 10 hours and a maximum of 14 hours between the morning and the evening dose. The first dose of the study medication was to be taken on day 1 in the evening. On day 8 (part 1) and day 85 (visit 7, part 2), no evening dose was to be administered.

Dose Group	Tablet 1	Tablet 2	Tablet 3
Placebo	0 mg	0 mg	0 mg
50 mg	40 mg	5 mg	5 mg
100 mg	40 mg	40 mg	20 mg

Duration of Treatment (or Duration of Study, if applicable):

The duration of participation per study patient in both part 1a and part 1b was approximately 5 weeks (including the screening period lasting 1 to 3 weeks prior to the first dose of study drug, 8 days of treatment and the 1-week follow-up period).

The duration of participation per study patient in part 2 was approximately 19 weeks (including the screening period lasting 1 to 3 weeks prior to the first dose of study drug, 12 weeks of treatment and the 4 weeks follow-up period).

Reference Product, Dose and Mode of Administration, Batch Numbers:

A placebo control was used in study part 2. Matching placebo tablets were manufactured by [redacted]. Study drug batches were released by Astellas Pharma Europe B.V., The Netherlands. Placebo batch numbers were [redacted] and [redacted].

The appearance of the ASP9831 tablets (e.g., the size, color, shape) of 5, 20 and 40 mg and placebo were identical and were packaged in identical aluminum/aluminum blisters.

Criteria for Evaluation:

Efficacy

Proof-of-principle (efficacy) was assessed in study part 2 only. The primary variable was the percentage change in serum ALT at the end of treatment at 12 weeks compared to baseline.

$$\text{Percentage change in serum ALT} = \frac{ALT_{12\ weeks} - (\text{minus})\ ALT_{baseline}}{ALT_{baseline}} \times 100(\%)$$

Secondary variables were the relative and absolute change from baseline to later assessments during the study, at the end of treatment and at the end of study as specified in the schedule of assessments for the following markers:

- Biomarkers for steatosis: SteatoTest, NashTest and adiponectin
- Biomarkers for inflammation: tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1 beta), interleukin-2 receptor (IL-2R), interleukin-6 (IL-6), interleukin-10 (IL-10) and C-reactive protein (CRP)
- Biomarkers for liver injury: ALT (including percentage of patients with normal ALT at week 12), aspartate aminotransferase (AST), AST/ALT ratio and the apoptosis marker cytokeratin 18 (CK-18)
- Biomarkers for liver fibrosis: FibroTest, hyaluronic acid, type III procollagen N-peptide, transforming growth factor beta (TGF-beta) and type IV collagen 7S domain
- Insulin resistance: serum fasting glucose and fasting insulin
- Clinical symptoms: Visual Analog Scale (VAS) for fatigue. Fatigue was assessed at visit 2 (baseline) and all following visits

Pharmacokinetics

In both part 1 and part 2 of the study, plasma samples were collected to determine the ASP9831 concentrations. In part 1, samples were collected over 24 hours after 8 days of twice daily dosing with 50 or 100 mg ASP9831. These data were analyzed using non-compartmental analysis. In part 2, a total of 4 plasma samples were collected up to 12 hours after dosing. Samples could be collected over different visits. Population pharmacokinetic analysis was conducted on the plasma concentration data of part 1 and part 2.

In part 1, dense pharmacokinetic sampling was performed on day 8 of the 8-day treatment course. Sparse plasma sampling was performed during the 12 weeks of treatment in part 2 [Table 1].

Table 1 Plasma ASP9831 Sampling Overview

Study Part	Treatment	Pharmacokinetic Sampling	n	Treatment Code
1a	50 mg BID, 8 days	Profile on day 8	7	50.1
1b	100 mg BID, 8 days	Profile on day 8	7	100.1
2a	50 mg BID, 12 weeks	Sparse	31	50.2
2b	100 mg BID, 12 weeks	Sparse	32	100.2

Study Part 1

The aim of the early exposure analysis in part 1 of the study was to explore the potential differences in pharmacokinetics between patients with NASH and healthy volunteers (data from study 9831-CL-0001). ASP9831 was administered to 2 cohorts of patients (7 patients each, part 1a and part 1b) and the following plasma pharmacokinetic parameters were derived using non-compartmental analysis (WinNonlin Professional version 5.01, Pharsight Corporation, Mountain View, CA, USA): area under the plasma concentration–time curve between two consecutive doses (AUC_{tau}), maximum ASP9831 plasma concentration (C_{max}), time to reach C_{max} (t_{max}), apparent body clearance after extravascular dosing (CL/F), terminal elimination half-life and apparent volume of distribution (V_z/F). For all calculations, actual sampling times were used. Details on how the pharmacokinetics parameters were calculated can be found in the statistical analysis plan (SAP) [Appendix 13.1.9].

Study Part 2

Plasma concentration data of ASP9831 collected during the study (part 1 and part 2) were subjected to a population pharmacokinetic analysis. The aim of this analysis was to develop a compartmental model of the plasma concentration versus time profiles and to evaluate the effects of selected covariates on the pharmacokinetic behavior of ASP9831. At a minimum, pharmacokinetic model parameters consisted of first order absorption rate constant (k_a), CL/F and V/F, but depending on the final model additional parameters could be needed as well. Derived (secondary) parameters were: t_{max}, C_{max}, trough plasma concentration (C_{trough}), AUC_{tau} and $t_{1/2}$.

Safety

Safety of ASP9831 was assessed by evaluation of the following:

- Adverse events occurring throughout the study.
- Physical examinations performed at visit 1 (screening), visit 2 (baseline) and at visit 5 (last study visit) in study part 1 and at visit 1 (screening), visit 2 (baseline), visit 7 and visit 8 (last study visit) in study part 2.
- Vital signs (performed at all visits): blood pressure and pulse rate obtained with the patient in supine position for at least 5 minutes.
- Safety laboratory assessments performed at visit 1 (screening), visit 2 (baseline) and at visit 5 (last study visit) in study part 1 and at each visit in part 2 (hematology, biochemistry, urinalysis, C-reactive protein, prothrombin time, activated partial thromboplastin time). Fasting glucose and fasting insulin were assayed at baseline only in study part 1 and at baseline, visit 5 (day 29), visit 7 (day 85) and visit 8 (last study visit) in study part 2.
- 12-lead ECG (performed at baseline/visit 2 and during treatment/visit 3 in study part 1 and at baseline/visit 2 and during treatment at visits 3, 5 and 7 in study part 2).
- Fibrinogen as biomarker for vascular damage (study part 2 only although it was also assayed once in study part 1).
- Investigators were requested to carefully monitor gastrointestinal symptoms which might be suggestive of colitis: diarrhea (> 3 loose stools per day for > 2 consecutive days), bloody diarrhea, passing of bright red blood without stool (patients were instructed to contact the investigator immediately if they observed blood in stools), reduction in hemoglobin of 1 g/dL or more compared to baseline, low-grade fever (≥ 37.7°C), abdominal distension, local signs of peritoneal irritation, moderate abdominal pain lasting more than 2 consecutive days especially in combination with other symptoms mentioned above and any other symptoms indicative of colitis.

  If 1 or more of these signs and symptoms were present and no other clear cause could be identified, the study medication was to be stopped immediately and a sigmoidoscopy with multiple biopsies was to be performed urgently. If the results were normal and the symptoms persisted, a complete colonoscopy was to be performed. The observation of the symptoms and the results of the sigmoidoscopy/colonoscopy were to be reported immediately using a serious adverse event (SAE) form. All results would then be forwarded to the independent DSMB who were to adjudicate the case.

  Gastrointestinal AEs such as nausea, vomiting and diarrhea were expected class effects of phosphodiesterase 4 (PDE4) inhibitors. These events were to be monitored thoroughly and reported as AEs. If a patient experienced moderate (affected normal daily activities) to severe (inability to perform daily activities) nausea, vomiting and/or diarrhea, for which no other cause could be identified and which, in the investigator's opinion, might have been related to the administration of the study medication, the investigator was advised to withdraw the patient from the study. If a patient suffered weight loss of more than 3 kg due to loss of appetite, nausea, vomiting and/or diarrhea, the investigator was advised to withdraw the patient from the study.

  Apart from gastrointestinal AEs, dizziness and headache were considered expected AEs based on the increased incidence of these AEs versus placebo in the previous multiple dose phase 1 study in healthy volunteers.

Statistical Methods:

The following is a summary of the statistical methodology used in this study. Comprehensive details of the statistical methods employed to analyze data in this study with changes made to the SAP after unblinding are provided in Appendix 13.1.9.

Descriptive statistics (number of observations, mean and SD, minimum, 25% quartile [Q1], median, 75% quartile [Q3] and maximum) were used to summarize continuous variables. For selected pharmacokinetic summaries, geometric mean and coefficient of variation (CV) were also presented. Descriptive statistics for categorical variables consisted of frequency and percentage of subjects in each category. Percentages by categories were based on the number of subjects with no missing data (i.e., will add up to 100%).

Disposition of Patients: The patient disposition included the number and percentage of patients in each treatment group: randomized, completed, discontinued study and reasons for study discontinuation, included in the FAS, PPS and SAF. The number of patients screened and the number of screen failures was tabulated. For part 1, similar analyses were conducted but the analysis sets were SAF and PKAS. Protocol violations/deviations that excluded patients from PPS were summarized by type of violations/deviations and treatment group for the FAS.

Demographics and Other Baseline Characteristics: Continuous demographic and baseline variables were summarized using descriptive statistics. Categorical demographic and baseline variables were described using absolute and relative frequencies.

Descriptive statistics for age, height, weight, body mass index (BMI), waist measurement, interval between biopsy and visit 2 and baseline variables at study entry were presented. Frequency tabulations for sex, race, fibrosis stage and type 2 diabetes were presented. This was done for the SAF, FAS, PPS and PKAS by treatment group. For PKAS, lean body weight, amount of body fat and body surface area were also presented.

Medical history was coded in MedDRA version 11.0 and summarized by system organ class and preferred term by treatment group for the SAF, FAS, PPS and PKAS.

Previous medications and concomitant medications (including post double-blind study treatment) were summarized by Anatomical Therapeutic Chemical (ATC) classification system (second and fourth level, chemical subgroup) and by treatment group for the SAF, FAS, PPS and PKAS.

Social history (alcohol and smoking habits) was summarized by treatment group for the SAF, FAS, PPS and PKAS. Number of patients by site and country was summarized.

For part 1, similar analyses were conducted but the analysis sets were SAF and PKAS.

Efficacy – Primary Analysis: The primary analysis was performed in the FAS on the mean percentage change in serum ALT at the end of treatment (at 12 weeks or at the last on-treatment value) compared to baseline.

Analysis of covariance (ANCOVA) was used to analyze the percentage change from baseline in serum ALT at week 12 with treatment group (including placebo) as a fixed factor. Site was included as a random factor. ALT, diabetes mellitus type 2 and BMI (< 30 or ≥ 30) at baseline were included in the model as factors. The hypotheses of the analyses were tested with a 2-sided significance level of 5% (type I error). The analysis first tested the following hypotheses:

H0: The mean change from baseline is the same in all treatment groups.

H1: The mean change from baseline is not the same in all treatment groups.

If H0 was rejected, the pair-wise comparisons by the ANCOVA were to be performed. Two-sided 95% CIs were provided.

Analysis of Secondary Efficacy Variables

Descriptive statistics for each visit were calculated for all secondary variables.

Pharmacokinetics: The PKAS was used for pharmacokinetic data analysis.

Predose blood samples were collected within 30 minutes prior to study drug administration. Their sampling times were set to 0 hours for pharmacokinetic derivations. Individual patient plasma ASP9831 concentrations were used to derive pharmacokinetics parameters using the non-compartmental methods appropriate for oral delivery.

Descriptive statistics (number of observations, mean and SD, minimum, median and maximum) were used to summarize plasma ASP9831 concentrations for each treatment arm at each scheduled time point. Descriptive summaries of plasma ASP9831 pharmacokinetic parameters were also provided for each treatment arm. Additionally, descriptive summaries of geometric means were provided for AUC_{tau}, C_{max}, C_{trough}, V_Z/F and CL/F.

Plots of mean plasma ASP9831 concentration at each scheduled time point were presented for each treatment arm. Individual patient plasma ASP9831 concentration at each scheduled time point overlay plots were provided for each treatment cohort separately. Linear and semi-log individual plasma ASP9831 concentration profiles by scheduled time point were produced for each patient separately. All available plasma concentration data from all patients were used for the graphical display.

The population pharmacokinetic models were developed and fitted to the data using NONMEM (version VI, release 1.1; Beal SL, Sheiner LB, Boeckmann AJ [1989–2006] NONMEM users guides, icon development solutions, Ellicott City, MD, USA) and analyzed using the statistical software packages R v2.9.1 and S-Plus® for Windows (version 6.2 Professional, release 1, Insightful Corporation, Seattle WA, USA).

The obtained minimum value of the objective function (MVOF), defined as minus 2 times the log-likelihood, was used for model comparisons. The first-order conditional estimate approximation with interaction (FOCE INTERACTION) was used for estimation. The same software environment was used for conducting VPC's and simulations. The random seed in NONMEM was set to an arbitrary 8-digit number.

Development of the model consisted of the following steps:

1. Selection of the structural and statistical model describing the pharmacokinetic profile of ASP9831 and identifying inter- and intrasubject variability.
2. Identification of significant covariates and inclusion in the structural model.
3. Evaluation of the final model by means of a visual predictive check.

Covariates evaluated were: sex (SEX), age (AGE), race (RACE), body weight (WGT), body fat (BFAT), lean body fat (LBWE), body mass index (BMI), height (HGT), body surface area (BSA), α_1-acid glycoprotein serum concentration (AGP), serum creatinine clearance (CRCL), ALT, AST, bilirubin (BILI), alkaline phosphatase (ALP), albumin (ALB), fibrosis stage according to central-external data (FSCE) and fibrosis stage according to local case report form data (FSLO).

LBWE was calculated as $1.10 * WGT - 128 (WGT/HGT)^2$ and amount of BFAT was calculated as $(1.2 * BMI + 0.23 * AGE - 16.2)/100 * WGT$ for males and as $(1.2 * BMI + 0.23 * AGE - 5.4)/100 * WGT$ for females, in which BMI was the body mass index, calculated as $WGT/(HGT)/100)^2$.

BSA was calculated as

$$\sqrt{WGT \cdot HGT/3600}$$

Serum CRCL was calculated according to the Cockcroft and Gault formula

$$\frac{(140 - AGE) * WGT * F}{\text{Plasma creatinine} * 0.8136'}$$

with F=1 for males and F=0.85 for females

Fibrosis stage was a categorical covariate with the following 6 categories: no fibrosis, stage 1a, stage 1b, stage 1c, stage 2 and stage 3.

Safety: The SAF was used for safety data analysis. All safety data were summarized using descriptive statistics and were listed and summarized in tabular form. No formal statistical testing was planned for the individual or combined AEs data. Frequency tables of treatment-emergent adverse events (TEAEs) by system organ class and preferred term were produced. Moreover, TEAEs were summarized by intensity (mild, moderate, severe) and by relationship to study drug (classified as not related, possibly and probably related).

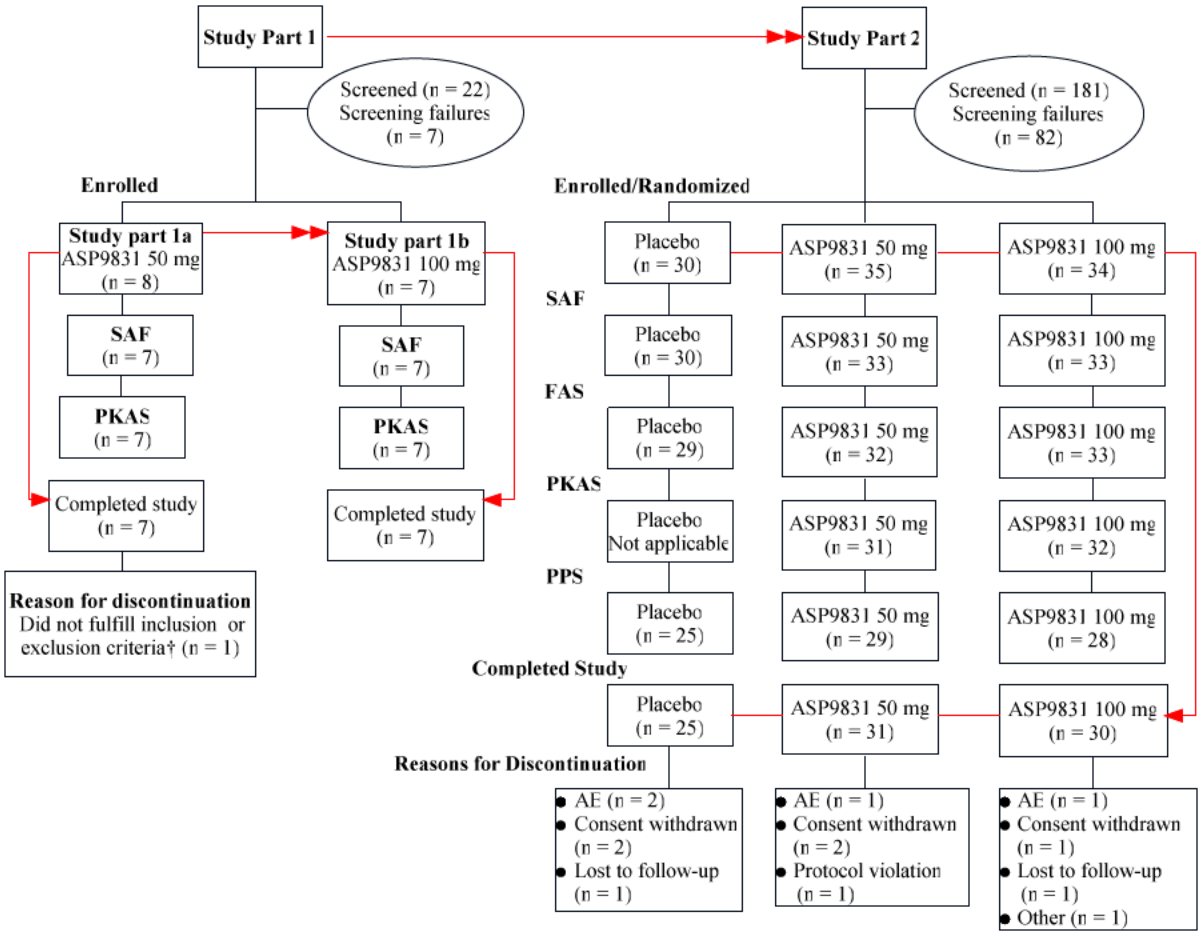
Summary of Results/Conclusions:

Analysis Sets and Patient Disposition

Fourteen of the 15 patients enrolled in part 1 and 86 of the 99 randomized patients in part 2 completed the study [Figure 5]. The reason for withdrawing the one patient in part 1 was due to noncompliance with eligibility criteria and occurred prior to study drug administration. Four of the 13 patients who were withdrawn in part 2 did so as result of an AE (2 placebo recipients and 2 ASP9831 recipients [1 in each dose group]). Details of these AEs are provided in the summary of safety data.

Overall, 12 of the 94 patients (12.8%) eligible for inclusion in the FAS in part 2 were excluded from the PPS (4 placebo recipients, 3 patients in the ASP9831 50-mg group and 5 patients in the ASP9831 100-mg group). The principal reasons for exclusion were administration of a prohibited concomitant medication (1 patient in both the placebo group and the ASP9831 50-mg group and 3 patients in the ASP9831 100-mg group) and treatment duration less than 9 weeks (3 placebo recipients, 1 patient in the ASP9831 50-mg group and 2 patients in the ASP9831 100-mg group) [Table 12.1.4].

Figure 5 Disposition of Patients and Analysis Sets



Enrolled: all patients who provided written informed consent, were determined eligible for enrollment based on screening procedures and were subsequently enrolled in the study (part 1)/were subsequently enrolled and randomized (part 2).

SAF: Safety Analysis Set; PKAS: Pharmacokinetics Analysis Set; FAS: Full Analysis Set; PPS: Per Protocol Set.

†Patient [redacted] met exclusion criterion number 13: Patient has a [redacted] which is not explained by previous Bacillus Calmette-Guerin vaccination [Appendix 13.2.2].

Source: Tables 12.1.1, 12.1.2 and 12.1.3.1 (part 1) and Tables 12.1.2, 12.1.3.1 and 12.1.7 (part 2); Appendix 13.2.1.2.

Demographics and Other Baseline Characteristics

The demographic profile of patients who received at least 1 dose of study drug in study part 1a and part 1b and in the 3 groups in study part 2 was comparable with respect to mean age, sex and racial distribution [Table 2].

The mean age was 53.9 years in part 1a and 50.9 years in part 1b and ranged from 43.1 to 46.2 years in part 2. The majority of patients in each group in both part 1 and part 2 were male (71.4% to 85.7% overall) and the study population was predominantly white (71.4% to 93.3% overall). In accordance with the protocol, all patients in study part 1a had NASH fibrosis stage F3 and all patients in study part 1b and study part 2 had NASH fibrosis stage F0 to F3. There was some variation across the 2 parts of the study in terms of age distribution but all groups were closely aligned in terms of BMI group (< 30 kg/m^2 and ≥ 30 kg/m^2) as well as mean BMI values.

The same distribution of demographic and baseline characteristics was seen in the PKAS in part 1a and part 1b and in both the ASP9831 treatment sequences in part 2. All patients who received at least 1 dose of study drug in both parts were eligible for the pharmacokinetic analysis [Table 12.1.5.4].

In part 2, a similar distribution of demographic and baseline characteristics was seen in the study groups included in the FAS [Table 12.1.5.2] and in the PPS [Table 12.1.5.3].

Table 2 Demographic and Baseline Characteristics

	Part 1		Part 2		
	ASP9831			ASP9831	
Parameter Category/Statistic	**1a: 50 mg (n = 7)**	**1b: 100 mg (n = 7)**	**Placebo (n = 30)**	**50 mg (n = 33)**	**100 mg (n = 33)**
Sex n (%)					
Male	6 (85.7)	5 (71.4)	22 (73.3)	24 (72.7)	24 (72.7)
Female	1 (14.3)	2 (28.6)	8 (26.7)	9 (27.3)	9 (27.3)
Age (years)					
n	7	7	30	33	33
Mean (SD)	53.9 (11.94)	50.9 (9.77)	43.1 (13.60)	45.9 (12.73)	46.2 (11.45)
Minimum - Maximum	33 - 70	33 - 62	20 - 67	22 - 68	21 - 78
Median	56.0	49.0	45.0	43.0	48.0
Q1 - Q3	47.0 - 62.0	48.0 - 60.0	33.0 - 53.0	38.0 - 56.0	37.0 - 53.0
Race n (%)					
White	6 (85.7)	5 (71.4)	28 (93.3)	31 (93.9)	28 (84.8)
Black	0	0	0	0	2 (6.1)
Asian	1 (14.3)	1 (14.3)	1 (3.3)	0	2 (6.1)
Other	0	1 (14.3)	1 (3.3)	2 (6.1)	1 (3.0)
BMI (kg/m^2)					
n	7	7	30	33	33
Mean (SD)	32.29 (3.422)	30.81 (3.743)	31.81 (5.647)	31.18 (4.949)	29.48 (5.152)
Minimum - Maximum	26.6 - 35.5	25.9 - 36.3	22.8 - 46.1	22.0 - 51.5	20.6 - 48.1
Median	31.60	31.20	29.55	30.40	28.10
Q1 - Q3	29.90 - 35.50	27.50 - 34.50	28.30 - 36.10	28.60 - 32.90	26.90 - 32.20
BMI Group (kg/m^2) n (%)					
< 30 kg/m^2	2 (28.6)	3 (42.9)	16 (53.3)	14 (42.4)	23 (69.7)
≥ 30 kg/m^2	5 (71.4)	4 (57.1)	14 (46.7)	19 (57.6)	10 (30.3)
Fibrosis Stage Group n (%)					
No fibrosis	0	0	4 (13.3)	1 (3.0)	6 (18.2)
Stage 1	0	2 (28.6)	12 (40.0)	9 (27.3)	12 (36.4)
Stage 2	0	2 (28.6)	7 (23.3)	16 (48.5)	8 (24.2)
Stage 3	7 (100)	3 (42.9)	7 (23.3)	7 (21.2)	7 (21.2)
Stage 4	0	0	0	0	0
Interval between biopsy and Visit 2 (Days)					
n	7	7	30	33	33
Mean (SD)	205.9 (138.44)	191.3 (106.11)	99.3 (78.61)	128.0 (120.46)	87.1 (62.01)
Minimum - Maximum	43 - 400	47 - 319	14 - 348	16 - 384	13 - 293
Median	127.0	173.0	81.0	76.0	69.0
Q1 - Q3	104.0 - 335.0	75.0 - 293.0	33.0 - 144.0	45.0 - 167.0	49.0 - 110.0
Diabetes type 2 n (%)	3 (42.9)	2 (28.6)	6 (20.0)	7 (21.2)	8 (24.2)

Safety Analysis Set: All enrolled (part 1) or all randomized (part 2) patients who took at least 1 tablet of study medication as confirmed by the returned medication.

Q1: 25% quartile; Q3: 75% quartile.

Source: Table 12.1.5.1.

Other Baseline Characteristics

The most commonly reported health conditions other than NASH in patients in part 1 were: hypercholesterolemia (4/7; 57.1%), type 2 diabetes and hypertension (each reported in 3/7; 42.9%) in part 1a, and dyslipidemia (5/7; 71.4%) in part 1b. All other medical history conditions were reported in 1 or 2 patients. Hypertension was the most commonly reported condition in all 3 treatment groups in part 2 (13/30; 43.3% in the placebo group, 15/33; 45.5% in the ASP9831 50-mg group and 9/33; 27.3% in the ASP9831 100-mg group) [Table 12.1.10.1].

Prior and Concomitant Medications

The therapeutic subgroups most commonly represented by prior and concomitant medications were the same in study part 1 and study part 2 [SAF in part 1 and part 2, Table 12.2.2.1.1; FAS in part 2, Table 12.2.2.1.2; PPS in part 2, Table 12.2.2.1.3 and PKAS in part 1 and part 2, Table 12.2.2.1.4].

In study part 1, the most commonly used prior medications in the SAF were lipid modifying agents (reported by 5/7 patients: 71.4% in part 1a and by 6/7 patients: 85.7% in part 1b). All other therapeutic subgroups of medication were reported by no more than 3 patients in either treatment group [Table 12.2.2.1.1].

In study part 2, the most commonly used prior medications in the SAF were agents acting on the renin-angiotensin system (reported 25% of patients overall) and drugs used in diabetes and lipid modifying agents (both reported by 22.9% of patients overall). Agents acting on the renin-angiotensin system were received at rates of 33.3% (placebo), 27.3% (ASP9831 50 mg) and 15.2% (ASP9831 100 mg). Drugs used for diabetes were reported at similar rates in the 3 treatment groups (20% of placebo recipients and 24.2% of ASP9831 recipients in both the 50-mg and 100-mg dose groups). However, 9.1% of patients in the ASP9831 100-mg group reported use of lipid modifying agents as compared to 20% of placebo recipients and 39.4% of patients in the ASP9831 50-mg group.

Study Drug Administration

All 14 dosed patients included in the SAF of study part 1 received treatment for 8 days as planned in the protocol. In study part 2, 76% of patients included in the SAF overall received treatment for 84 days (70% in the placebo group and 78.8% in both the 50 mg and 100 mg dose groups of ASP9831 [Table 12.2.1.1].

Treatment compliance was to be assessed at visits 3, 4, 5, 6 and 7. Patients were to bring all medication wallets received at the previous visit to the clinic. The investigator collected the medication wallets and recorded the number of tablets returned in the study files and in the electronic case report form (eCRF). Mean treatment compliance was 87.6% in study part 1 (87.7% in ASP9831 50 mg recipients and 87.5% in ASP9831 100-mg recipients). In part 2, overall mean treatment compliance was 97.7% (96.4% in the placebo group, 97.8% in ASP9831 50-mg recipients and 98.9% in ASP9831 100-mg recipients) [Table 12.2.1.1].

Pharmacokinetics

The full report of methods and results of pharmacokinetic modeling of ASP9831 is provided as Attachment 2 of this report.

Study part 1, non-compartmental analysis

In part 1a and part 1b, patients received 50 mg or 100 mg ASP9831 BID for 8 days, respectively. After the (last) morning dose on day 8, plasma samples were collected for 24 hours to determine the steady state pharmacokinetics of ASP9831.

The descriptive statistics of these parameters are provided in Table 3. The mean plasma concentration time profiles are shown in Figure 6.

Since the mean AUC_{tau} following 50 mg BID in study part 1a was 4622 hr*ng/mL (below the mean AUC value of 18900 hr*ng/mL following 100 mg BID in healthy volunteers), study part 1b was performed as planned.

In patients with NASH, ASP9831 was rapidly absorbed under fed conditions; the mean t_{max} was 1.26 hours for the 50-mg BID group and 1.71 hours for the 100-mg BID group. In addition, a dose proportional increase in C_{max} and AUC_{tau} was observed when dose was increased from 50 mg BID to 100 mg BID. The mean C_{max} values were 1465 and 3320 ng/mL for the 50- and 100-mg BID dosing, respectively. The AUC_{tau} (calculated over 12 hours) was 4622 hr*ng/mL for the 50-mg BID dose group and 10825 h*ng/mL for the 100 mg BID dose group. No dose dependency was observed for $t_{1/2}$, CL_{SS}/F and V_Z/F.

Table 3 Summary Statistics of the ASP9831 Plasma Pharmacokinetic Parameters after Multiple Oral Doses of ASP9831 Under Fed Conditions (Study Part 1)

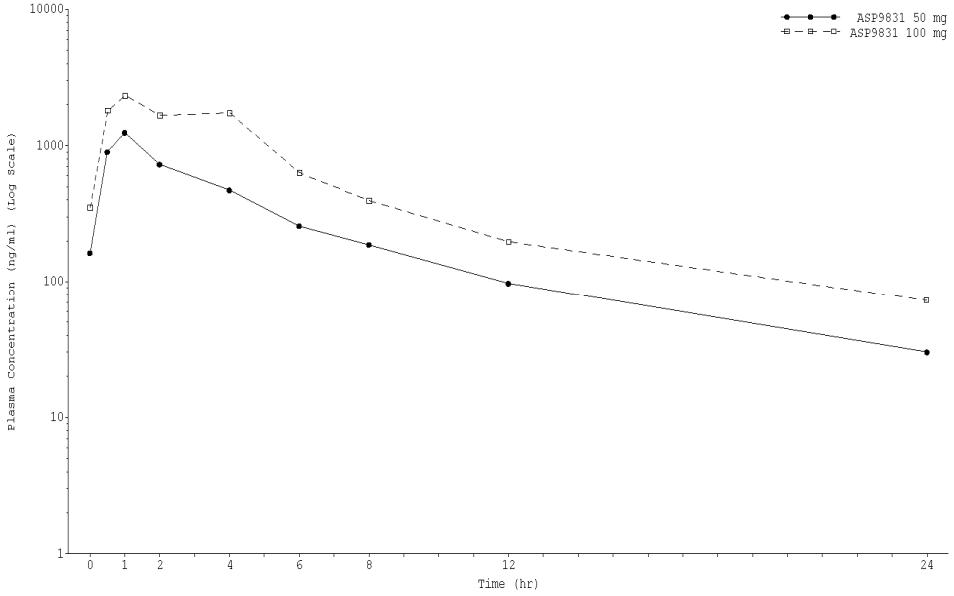
Parameter	Statistic	ASP9831	
		50 mg (n = 7)	100 mg (n = 7)
t_{max} (h)	n	7	7
	Mean (SD, CV%)	1.26 (1.23, 98%)	1.71 (1.58, 92%)
C_{max} (ng/mL)	n	7	7
	Mean (SD, CV%)	1465 (503, 34%)	3320 (1098, 33%)
AUC_{tau} (hr*ng/mL)	n	7	7
	Mean (SD, CV%)	4622 (1831, 40%)	10825 (4105, 38%)
$t_{1/2}$ (h)	n	7	5
	Mean (SD, CV%)	6.47 (1.71, 26%)	7.01 (1.77, 25%)
CL_{SS}/F (L/h)	n	7	7
	Mean (SD, CV%)	12.2 (4.25, 35%)	10.3 (3.52, 34%)
V_Z/F (L)	n	7	5
	Mean (SD, CV%)	113 (47.1, 42%)	114 (47.2, 42%)
C_{trough} (ng/mL)	n	7	7
	Mean (SD, CV%)	97.1 (56.7, 58%)	197 (122, 62%)

CV%: coefficient of variation expressed as percentage.

PKAS: All patients from the SAF with sufficient plasma drug concentration data to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

Source: Table 12.4.2

Figure 6 Mean ASP9831 Plasma Concentration Time Profiles after Multiple Oral Doses (Day 8) of ASP9831 in Patients With NASH Under Fed Conditions



PKAS: All patients from the SAF with sufficient plasma drug concentration data to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

Source: Figure 12.4.2.

Comparison to Healthy Subjects (Study 9831-CL-0001)

The mean, as well as the median, t_{max} was about 2-fold longer in patients with NASH compared to healthy subjects. The mean C_{max} was about 2-fold lower in patients compared to healthy subjects, possibly as a result of the slower absorption. The difference in t_{max} and C_{max} between healthy subjects and patients was likely caused by the effect of food on the absorption of ASP9831. AUC_{tau}, CL/F,V/F and $t_{1/2}$ were comparable in patients as compared to healthy subjects. In the healthy volunteer study, ASP9831 was dosed under both fasted and fed conditions, whereas in the current study, ASP9831 was dosed under fed conditions. The food effect part of study 9831-CL-0001 confirmed that when given under fed conditions, the t_{max} increases and the C_{max} decreases. The administration of ASP9831 with a high fat breakfast resulted in a 1.7-fold increase in t_{max} and a 1.5-fold decrease in C_{max} (fed / fasted = 0.668; CI =0.551; 0.811), whereas AUC and $t_{1/2}$ were unaffected. This indicated that the differences in t_{max} and C_{max} observed after multiple doses of ASP9831 between patients and healthy subjects were caused by the fed conditions.

Study Part 2, Population Pharmacokinetics Results

Population pharmacokinetics analysis was used to model the data of parts 1 and 2 of the study. No data from part 1 were excluded from the analysis (i.e., no outliers were observed). Data from 2 subjects in part 2 were excluded from the analysis and 1 sample was excluded from an additional 2 subjects.

In the first step, a population pharmacokinetics model without covariates was developed. A 2-compartmental model with first order absorption and a constant CV residual error described the plasma concentration of ASP9831 well. A lag time could not be estimated. Using forward inclusion, intersubject variability was added on absorption rate constant, clearance and volume of central compartment. Subsequently, covariates were added iteratively using the forward selection cycle as described in the SAP. Covariates were included in the model only when they were significant at the 0.05 level. Structural parameters were assumed to be linearly dependent on covariates, e.g.,

$$CL_i = (TVCL + \beta*(COVi-Median(COV))) * \exp(\eta_{CL})$$

The parameter table of this 'full' model is provided in Table 4. It shows there was a positive relationship between body weight and clearance and there were negative relationships between AST and clearance, bilirubin and clearance and between AST and volume of central compartment. All covariates were benchmarked using backward deletion at the P-value=0.001 level. Covariates that were determined to be not significant were removed from the model. This resulted in the final model. In the final model, clearance depended on weight and AST:

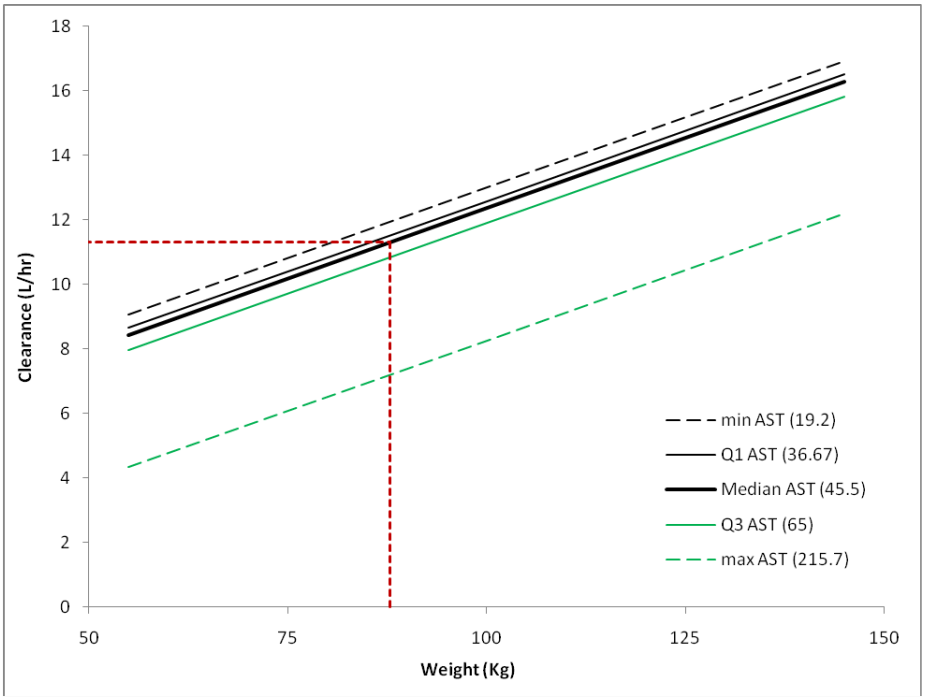
$$\text{Clearance (L/h)} = 11.3 + 0.0873\ (\text{Weight} - 87.7) - 0.0241\ (\text{AST} - 45.5)$$

A graphic representation of this dependency on both weight and AST is provided in Figure 7. The red dotted line represents the median weight and its accompanying clearance.

Population pharmacokinetic analysis of the ASP9831 plasma data revealed that pharmacokinetics could be described by a linear 2-compartment model with first order absorption. The inter-subject variability was described by a log-normal distribution and could be estimated for rate of absorption (Ka), clearance (CL/F), and the central volume of distribution (V2/F). Statistically significant covariates found were body weight and AST on CL/F. CL/F increased with increasing body weight (by 0.87 l/h per10 kg), and decreased with decreasing AST (by 0.24 l/h per 10 U/L). An overview of the final model parameters is provided in [Table 4].

Figure 8 plots the estimated clearances along with the estimated dependencies. It shows there were clear dependencies between clearance and Weight and between clearance and AST, and that linearity is a reasonable assumption.

Figure 7 Clearance as Function of Weight and AST



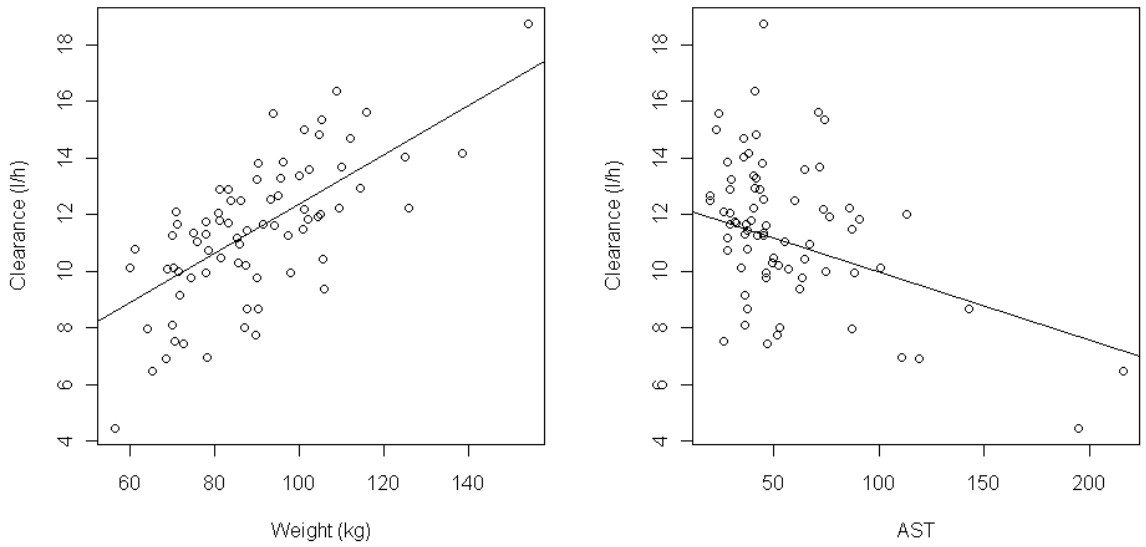
PKAS: All patients from the SAF with sufficient plasma drug concentration data to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

Table 4 Parameter Table of the Final Model

Parameter	Interpretation	Estimate	Standard Error
K_a	Absorption rate	2.15	0.386
CL/F	Clearance	11.3	0.485
V2/F	Volume of central compartment	18.3	1.96
V3/F	Volume of peripheral compartment	36.5	2.96
Q/F	Intercompartmental clearance	5.54	0.514
βW,CL	Linear weight dependency for CL	0.0873	0.0177
βA,CL	Linear AST dependency for CL	-0.0241	0.00727
OM(KA)	Variance IIV(KA)	1.55	0.414
OM(CL)	Variance IIV(CL)	0.0316	0.00726
OM(V2)	Variance IIV(V2)	0.119	0.0421
SIGMA	Variance CCV residual error	0.176	0.0206

PKAS: All patients from the SAF with sufficient plasma drug concentration data to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

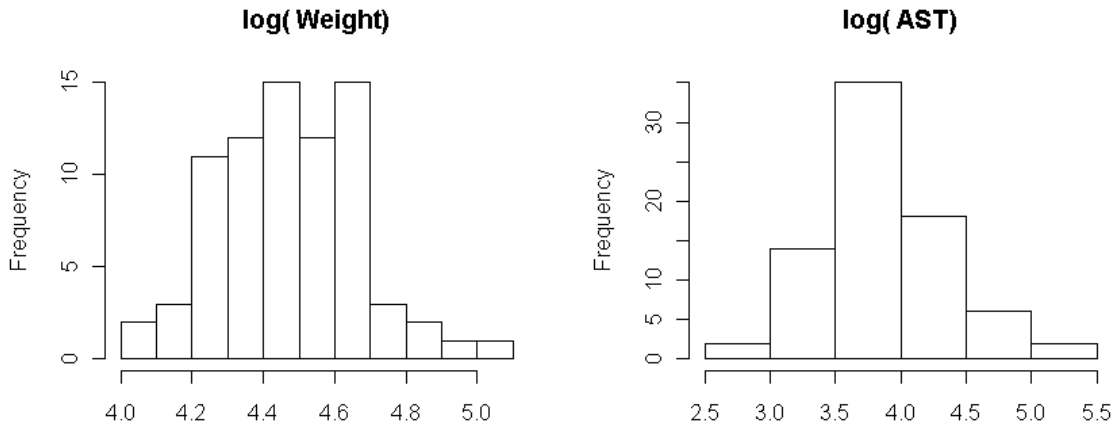
Figure 8 Estimated Individual Clearances and Estimated Population Clearances



PKAS: All patients from the SAF with sufficient plasma drug concentration data to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

Visual Predictive Check of the Final Model
Visually predictive checks were performed to further qualify the model, and showed that the final model was able to accurately describe the pharmacokinetics in the 50- and 100 mg dose groups in study parts 1 and 2. Covariates 'weight' and 'AST' were simulated from lognormal distributions to reflect demographics as seen in the dataset. Figure 9 shows this was a reasonable assumption.

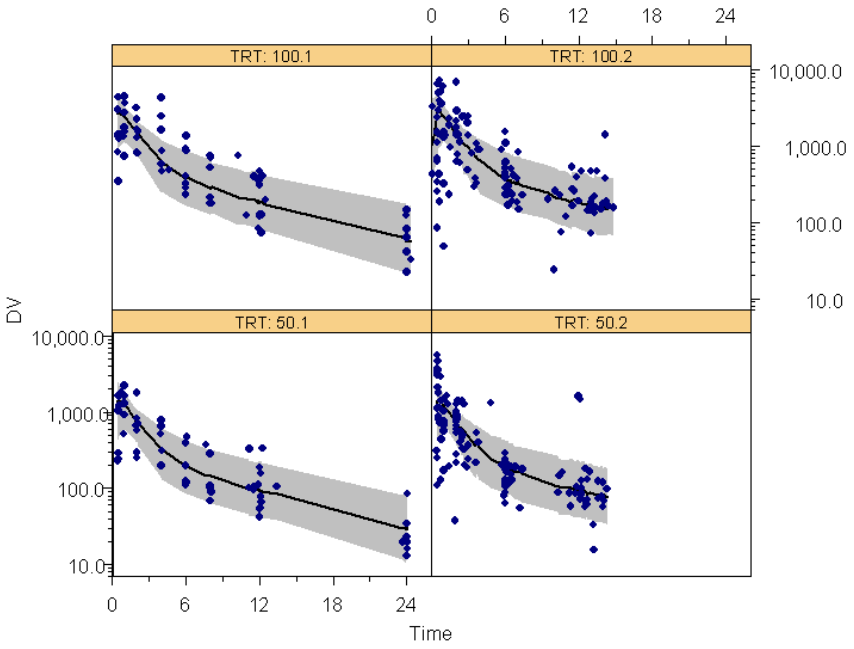
Figure 9 Histograms of Covariates Weight and AST



PKAS: All patients from the SAF with sufficient plasma drug concentration data to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

The visually predictive check showed that the predicated median concentration curve described the data without bias for all 4 treatment groups (50-mg and 100-mg treatment groups of study parts 1 and 2) [Figure 10]. About 90% of the data from part 1 fell in the 90% prediction interval, indicated by the shaded area (panels 100.1 and 50.1 in the figure). For the sparse sampling data (panels 100.2 and 50.2), variability was slightly under predicted, especially within the 2 hours after the study drug administration. This was considered most likely due to the inaccuracies in reported times of study drug administration. Since part 2 consisted of sparse sampling, the simulated concentrations were plotted against time after the last dose.

Figure 10 Visual Predictive Check of Final Model



PKAS: All patients from the SAF with sufficient plasma drug concentration data to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

Note: The observed data still include outliers.

Descriptive Statistics of Plasma ASP9831 Pharmacokinetic Parameters

The final model was used to estimate the individual values of the pharmacokinetic parameters. Non-compartmental analysis was done for part 1 data only [Table 3]. In general, results from the population pharmacokinetics modeling and the non-compartmental analysis corresponded well [Table 5].

The largest deviation was for the mean trough concentration for the 100-mg dose group: 31%. The mean C_{max} value for the same dose group deviated 28%. The majority of these differences can be attributed to the fact that estimates for the pharmacokinetic parameters for patients in part 1 were not independent from the parameter estimates of patients in part 2. Since for most patients (80%), only sparse sampling data were available, the absorption rate constant could not be estimated very precisely and therefore estimates for C_{max} and C_{trough} in part 1 deviated to some extent from the non-compartmental analysis. This should be taken into account when performing future pharmacokinetic simulations. Note that for the 50-mg dose group in part 1, the estimates for C_{max} and C_{trough} differed less than 15%.

Table 5 Comparison of Descriptive Statistics Part 1

Parameter	Statistic	50 mg (n = 7)		100 mg (n = 7)	
		NCA	Pop PK	NCA	Pop PK
CL_{ss}/F (L/h)	Mean (SD, CV%)	12.2 (4.25, 35%)	11.8 (2.60, 22%)	10.3 (3.52, 34%)	10.8 (3.10, 29%)
V_Z/F (L)	Mean (SD, CV%)	113 (47.1, 42%)	121 (16.0, 13%)	114 (47.2, 42%)	116 (19.0, 16%)
t_{max} (h)	Mean (SD, CV%)	1.26 (1.23, 98%)	1.09 * (0.60, 55%)	1.71 (1.58, 92%)	1.20 ** (0.56, 47%)
C_{max} (ng/mL)	Mean (SD, CV%)	1465 (503, 34%)	1245 * (504, 40%)	3320 (1098, 33%)	2406 ** (837, 35%)
AUC_{tau} (hr*ng/mL)	Mean (SD, CV%)	4622 (1831, 40%)	4453 (1176, 26%)	10825 (4105, 38%)	9916 (2946, 30%)
$t_{1/2}$ (h)	Mean (SD, CV%)	6.47 (1.71, 26%)	7.26 * (0.79, 11%)	7.01 (1.77, 25%)	7.63 (1.03, 13%)
C_{trough} (ng/mL)	Mean (SD, CV%)	97.1 (56.7, 58%)	105 (58.1, 55%)	197 (122, 62%)	257 *** (155, 60%)

PKAS: All patients from the SAF with sufficient plasma drug concentration data to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

NCA: non-compartmental analysis; Pop PK: population pharmacokinetics; CV%: coefficient of variation percentage.

* Deviates more than 10% from NCA value.

** Deviates more than 20% from NCA value.

*** Deviates more than 30% from NCA value.

Source: Table 12.4.2

Efficacy Results

Baseline Biomarker Status in Study Part 2

To be eligible for inclusion in study part 2, patients were to have ALT levels at screening of at least 1.5 times the ULN or > 60 IU/L (local laboratory) on 1 occasion in the previous 6 months and no documented normal value in the previous year. In the FAS, the 3 groups of patients were comparable with respect to baseline liver enzyme status and other biomarkers with respect to liver status [Table 6]. This observation was also true for patients eligible for inclusion in the PPS [Table 12.1.6.3].

Table 6 Baseline Biomarkers Status

Parameter	Placebo (n = 29)	ASP9831	
		50 mg (n = 32)	100 mg (n = 33)
ALT (U/L) n	29	32	33
Mean (SD)	107.0 (57.51)	96.8 (50.91)	93.5 (50.11)
Minimum - Maximum	37 - 274	39 - 254	31 - 247
Q1 - Q3	70.0 - 133.0	63.0 - 108.0	62.0 - 97.0
Median	90.0	80.5	80.0
AST (U/L) n	29	32	33
Mean (SD)	59.4 (31.22)	57.8 (32.62)	56.9 (30.09)
Minimum - Maximum	20 - 143	18 - 138	20 - 141
Q1 - Q3	38.0 - 76.0	36.0 - 62.5	35.0 - 82.0
Median	48.0	48.0	44.0
AST/ALT ratio n	29	32	33
Mean (SD)	0.602 (0.2427)	0.610 (0.2153)	0.636 (0.2399)
Minimum - Maximum	0.26 - 1.14	0.32 - 1.37	0.34 - 1.64
Q1 - Q3	0.430 - 0.730	0.480 - 0.685	0.490 - 0.700
Median	0.520	0.560	0.580
FibroTest n	29	32	33
Mean (SD)	0.280 (0.2130)	0.351 (0.2128)	0.293 (0.2320)
Minimum - Maximum	0.07 - 0.88	0.07 - 0.86	0.03 - 0.81
Q1 - Q3	0.090 - 0.390	0.165 - 0.490	0.090 - 0.400
Median	0.230	0.310	0.220
SteatoTest n	28	30	28
Mean (SD)	0.765 (0.1322)	0.724 (0.1481)	0.710 (0.1870)
Minimum - Maximum	0.43 - 0.98	0.31 - 0.98	0.19 - 0.95
Q1 - Q3	0.700 - 0.865	0.610 - 0.820	0.640 - 0.850
Median	0.770	0.750	0.740
NashTest n	28	30	28
Mean (SD)	0.509 (0.1270)	0.525 (0.1369)	0.500 (0.1667)
Minimum - Maximum	0.25 - 0.75	0.25 - 0.75	0.25 - 0.75
Q1 - Q3	0.500 - 0.500	0.500 - 0.500	0.500 - 0.500
Median	0.500	0.500	0.500

Full Analysis Set (FAS): All patients in part 2 who took at least 1 tablet of study medication and had at least 1 post-baseline value of ALT.

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Source: Table 12.1.6.2

Primary Efficacy Endpoint: Percentage Change of ALT

The primary analysis was performed in the FAS on the mean percentage change in serum ALT at the end of treatment (at 12 weeks or at the last on-treatment value) compared to baseline. The relative day was based on the date for visit 2. Day 1 was the date for visit 2.

Neither ASP9831 50 mg nor ASP9831 100 mg showed a significant decrease in ALT compared to placebo [Table 7]. Results of the analysis based on the PPS were consistent with those seen in FAS [Table 12.3.1.1.2, Table 12.3.4.1.2 and Table 12.3.4.2.2].

Table 7 Percentage Change in Serum ALT at the End of Treatment (12 Weeks)

Parameter	Placebo (n = 29)	ASP9831 50 mg (n = 32)	ASP9831 100 mg (n = 33)	Overall Comparison P-value	ASP9831 minus Placebo 50 mg P-value Estimate [CI]	ASP9831 minus Placebo 100 mg P-value Estimate [CI]
Baseline (U/L) Mean (SD)	107.0 (57.51)	96.8 (50.91)	93.5 (50.11)	NA	NA	NA
% change† Mean (SD)	-13.33 (26.034)	-1.26 (35.115)	-9.30 (32.013)	0.419	0.228 9.29 [-5.92, 24.50]	0.857 1.37 [-13.68, 16.42]

NA: not applicable; ALT: alanine aminotransferase.

Full Analysis Set (FAS): All patients in part 2 who took at least 1 tablet of study medication and had at least 1 post-baseline value of ALT.

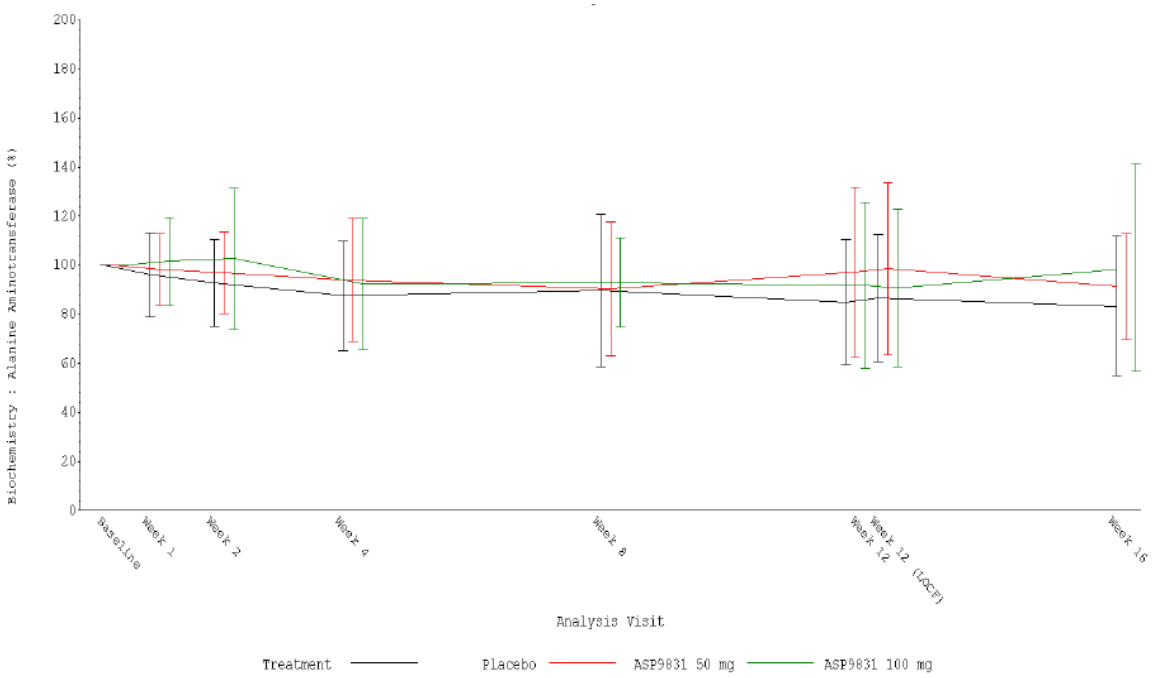
Negative percentages indicate clinical improvement.

†These data based on last observation carried forward.

Source: Table 12.3.1.1.1, Table 12.3.4.1.1 and Table 12.3.4.2.1

Plots of mean values (± SD) show the stable and similar serum levels of ALT over the course of the study in following placebo, ASP9831 50 mg and ASP9831 100 mg [Figure 11].

Figure 11 Mean ALT Values (SD) of Normalized Values of ALT by Visit



Full Analysis Set (FAS): All patients in part 2 who took at least 1 tablet of study medication and had at least 1 post-baseline value of ALT.

Source: Figure 12.3.1.4.1

Primary Efficacy Endpoint Under Fasting Conditions

Because some blood samples were obtained under non-fasting conditions (protocol deviation), analysis of the primary endpoint was repeated for the FAS using only those ALT results obtained under fasting conditions [Table 8]. Similar results indicated that ALT values obtained from non-fasting blood samples did not bias the final results.

Table 8 Percentage Change in Serum ALT at the End of Treatment (12 Weeks) under Fasting Conditions

Parameter	Placebo (n = 28)	ASP9831 50 mg (n = 30)	ASP9831 100 mg (n = 30)	Overall Comparison P-value	ASP9831 minus Placebo 50 mg P-value estimate [CI]	ASP9831 minus Placebo 100 mg P-value estimate [CI]
Baseline (U/L) Mean (SD)	108.3 (58.11)	97.4 (52.44)	93.6 (51.48)	NA	NA	NA
% change†					0.744	0.764
Mean (SD)	-13.60 (25.478)	-10.23 (26.708)	-8.86 (33.103)	0.823	-2.24 [-15.86, 11.38]	2.07 [-11.59, 15.72]

Full Analysis Set (FAS): All patients in part 2 who took at least 1 tablet of study medication and had at least 1 post-baseline value of ALT.

Negative percentages indicate clinical improvement.

ALT: alanine aminotransferase; NA: not applicable.

†These data based on last observation carried forward.

Source: Table 12.3.1.1.1, Table 12.3.4.1.1 and Table 12.3.4.2.1

Percentage Change in AST at Week 12

No statistical significance was shown for the mean percentage change in AST values following either the 50-mg or 100-mg ASP9831 treatment regimen [Table 9]. Results of the analysis based on the PPS were consistent with those seen in FAS [Table 12.3.1.1.2, Table 12.3.4.1.2 and Table 12.3.4.2.2].

Table 9 Percentage Change in Serum AST at the End of Treatment (12 Weeks)

Parameter	Placebo (n = 29)	ASP9831 50 mg (n = 32)	ASP9831 100 mg (n = 33)	Overall Comparison P-value	ASP9831 minus Placebo 50 mg P-value estimate [CI]	ASP9831 minus Placebo 100 mg P-value estimate [CI]
Baseline (U/L) Mean (SD)	59.4 (31.22)	57.8 (32.62)	56.9 (30.09)	NA	NA	NA
% change†					0.094	0.745
Mean (SD)	-8.62 (27.519)	11.88 (72.057)	-4.47 (34.923)	0.202	21.57 [-3.75, 46.88]	4.12 [-20.97, 29.21]

Full Analysis Set (FAS): All patients in part 2 who took at least 1 tablet of study medication and had at least 1 post-baseline value of ALT.

Negative percentages indicate clinical improvement.

AST: aspartate aminotransferase; NA: not applicable.

†These data were based on last observation carried forward.

Source: Table 12.3.1.1.1, Table 12.3.4.1.1 and Table 12.3.4.2.1

Subgroup Analysis for Percentage Change in ALT from Baseline

Summary statistics for the percentage change from baseline in ALT values by subgroup indicated no obvious effect of any of the integrated factors on the primary efficacy variable [Table 10]. There was no evident site effect on the primary variable when analysis was performed according to study site [Table 12.3.6.1].

Table 10 Subgroup Analysis for the Percentage Change from Baseline in ALT Value at the End of Treatment (12 Weeks)

Subgroup	Placebo		ASP9831 50 mg		ASP9831 100 mg	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Age: < 65 years	28	-11.91 (25.345)	29	1.21 (35.553)	32	-10.20 (32.102)
Age: ≥ 65 years	1	-53.05	3	-25.10 (21.788)	1	19.35
Sex: Male	21	-7.86 (25.786)	23	-8.44 (21.565)	24	-13.02 (32.153)
Sex: Female	8	-27.68 (22.048)	9	17.10 (54.515)	9	0.60 (31.231)
Fibrosis stage: No fibrosis	4	-14.74 (14.038)	1	-33.33	6	-15.28 (39.778)
Fibrosis stage: 1	12	-16.47 (29.364)	9	-1.13 (22.631)	12	-9.33 (26.853)
Fibrosis stage: 2	7	-10.40 (25.132)	15	2.47 (43.360)	8	-18.00 (19.532)
Fibrosis stage: 3	6	-9.51 (31.108)	7	-4.83 (32.862)	7	5.81 (44.463)
Baseline ALT: < 70 U/L	7	-20.23 (28.513)	10	-4.59 (20.497)	11	0.15 (26.737)
Baseline ALT: 70 - < 100 U/L	10	-7.05 (23.013)	8	-8.20 (29.013)	14	-11.50 (39.276)
Baseline ALT: ≥ 100 U/L	12	-14.53 (27.943)	13	3.78 (47.587)	8	-18.44 (23.524)
No diabetes type 2	23	-12.01 (28.359)	26	-2.93 (37.034)	25	-7.56 (34.699)
Diabetes type 2	6	-18.38 (14.771)	6	5.99 (26.640)	8	-14.76 (22.625)
BMI group: < 30 kg/m^2	16	-13.46 (25.249)	13	-3.00 (48.978)	23	-7.33 (34.304)
BMI group: ≥ 30 kg/m^2	13	-13.17 (28.010)	19	-0.06 (22.818)	10	-13.83 (27.104)

Full Analysis Set (FAS): All patients in part 2 who took at least 1 tablet of study medication and had at least 1 post-baseline value of ALT.

These data were based on last observation carried forward.

ALT: alanine aminotransferase; BMI: body mass index.

Source: Table 12.3.6.1

Summary Statistics of Actual Values of Biomarkers

A number of biochemical biomarkers that were either related to downstream pharmacology of the target or are relevant to NASH were measured as secondary parameters for exploratory purposes. For the secondary parameters measured, no ASP9831 prominent differences were noted compared to placebo. Moreover, no ASP9831 treatment related trends or signals, more than that of the inherent variability for each biomarker, were identified for in any of the figures produced [Figure 12.3.1.1.1 through Figure 12.3.2.2.2]. It can be concluded that ASP9831 had no effects on any of the biomarkers measured.

Summary Statistics of VAS for Presence and Severity of Fatigue

Mean values for the presence and severity of fatigue assessed at baseline and at all subsequent time points in all 3 groups evidenced no marked changes or differences in any of the three groups [Table 12.3.8.1.1].

	Baseline	Week 12 (LOCF)
Placebo	6.22 ± 2.804 cm	5.94 ± 3.125 cm
ASP9831 50 mg	5.70 ± 3.393 cm	5.92 ± 3.150 cm
ASP9831 100 mg	6.40 ± 2.905 cm	6.38 ± 3.158 cm

Safety Results

Treatment-emergent Adverse Events Study Part 1

Safety data from study part 1 were considered when making the decision to proceed with study part 2. During study part 1, 4/7 (57.1%) ASP9831 50-mg recipients and 6/7 (85.7%) ASP9831 100-mg recipients experienced at least 1 TEAE. No death, other SAEs or AEs resulting in discontinuation occurred [Table 12.6.1.1].

All TEAEs in the 50-mg dose group were gastrointestinal disorders (all reported in 1 patient) with the exception of 1 report of a single episode of glycosuria [Table 12.6.1.2 and Appendix 13.2.7.1]. All TEAEs were graded mild or moderate in severity and all were considered study drug related with the exception of the glycosuria event (categorized as not related and of mild intensity) [Table 12.6.1.3 and Table 12.6.1.4]. All TEAEs reported in part 1 were categorized as resolved/recovered [Appendix 13.2.7.1].

Treatment-emergent Adverse Events Study Part 2

The incidence of TEAEs varied from 60% in placebo recipients, 75.8% in the ASP9831 50-mg dose cohort to the highest incidence of 87.9% of patients in the ASP9831 100-mg dose cohort [Table 11].

Table 11 Overview of the Incidence and Number of Treatment-emergent Adverse Events in Study Part 2

		ASP9831	
	Placebo (n = 30)	50 mg (n = 33)	100 mg (n = 33)
Parameter	**n (%)**	**n (%)**	**n (%)**
Incidence of adverse events	18 (60.0)	25 (75.8)	29 (87.9)
Number of adverse events	61	91	85
Incidence of drug related† adverse events	11 (36.7)	16 (48.5)	26 (78.8)
Number of drug related† adverse events	25	50	54
Incidence of deaths	1 (3.3)	0	0
Incidence of serious adverse events	3 (10.0)	0	0
Incidence of drug related† serious adverse events	1 (3.3)	0	0
Number of drug related† serious adverse events	1	0	0
Incidence of adverse events leading to permanent discontinuation of study drug	2 (6.7)	1 (3.0)	1 (3.0)
Number of adverse events leading to permanent discontinuation of study drug	2	1	1
Incidence of drug related adverse events† leading to permanent discontinuation of study drug	1 (3.3)	1 (3.0)	1 (3.0)
Number of drug related† adverse events leading to permanent discontinuation of study drug	1	1	1

SAF: Patients who took at least 1 tablet of study medication as confirmed by returned medication.

† Attributed a possible or probable relationship to study drug by the investigator or records where relationship was missing (In this study no relationship attribution was missing).

Source: Table 12.6.1.1 and Appendix 13.2.7.1

The most commonly reported TEAEs in the placebo group were headache, fatigue and asthenia (each event reported in 16.7% of the patients) [Table 12]. Headache (reported in 21.2% of patients) and diarrhea and fatigue (each reported in 15.2% of patients) were the most common AEs in the ASP9831 50-mg dose group. Diarrhea (reported in 21.2% of patients) and nausea (reported in 30.3% of patients) were the most common AEs in the ASP9831 100-mg dose group.

At least 1 study drug related TEAE was reported in 36.7% of patients in the placebo group, 48.5% of patients in the ASP9831 50-mg dose group and in 78.8% of patients in the ASP9831 100-mg dose group [Table 12.6.1.3].

All TEAEs in all 3 treatment groups were categorized as mild or moderate severity with the exception of 1 case of severe headache and 1 severe anaphylactic shock in the placebo group and 1 case of severe muscle spasms in the ASP9831 50-mg dose group [Table 12.6.1.4 and Appendix 13.2.7.1].

Placebo Patient [redacted] on day 59 which was not considered drug related. This event resulted in the [redacted] on day 59.

Patient [redacted] with onset on day 13 and resolution on day 14. The event was attributed a possible relationship to study drug.

ASP9831 50 mg Patient [redacted] with onset on day 3 and resolution on day 6. The event was attributed a possible relationship to study drug and [redacted].

Table 12 Treatment-emergent Adverse Events Reported in at Least 2 Patients in Any Group During Study Part 2

System Organ Class (MedDRA v11.0) Preferred Term	Placebo (n = 30) n (%)	ASP9831 50 mg (n = 33) n (%)	ASP9831 100 mg (n = 33) n (%)
Gastrointestinal disorders	**9 (30.0)**	**14 (42.4)**	**22 (66.7)**
Diarrhoea	2 (6.7)	5 (15.2)	7 (21.2)
Nausea	0	2 (6.1)	10 (30.3)
Abdominal pain	1 (3.3)	4 (12.1)	4 (12.1)
Flatulence	1 (3.3)	3 (9.1)	4 (12.1)
Dyspepsia	1 (3.3)	2 (6.1)	4 (12.1)
Frequent bowel movements	2 (6.7)	2 (6.1)	2 (6.1)
Vomiting	0	0	4 (12.1)
Abdominal distention	1 (3.3)	1 (3.0)	2 (6.1)
Abdominal pain upper	2 (6.7)	1 (3.0)	1 (3.0)
Nervous system disorders	**6 (20.0)**	**10 (30.3)**	**7 (21.2)**
Headache	5 (16.7)	7 (21.2)	5 (15.2)
Paraesthesia	0	2 (6.1)	0
Dizziness	2 (6.7)	0	1 (3.0)
General disorders and administration site conditions	**10 (33.3)**	**9 (27.3)**	**4 (12.1)**
Fatigue	5 (16.7)	5 (15.2)	3 (9.1)
Asthenia	5 (16.7)	1 (3.0)	2 (6.1)
Pyrexia	0	3 (9.1)	0
Musculoskeletal and connective tissue disorders	**3 (10.0)**	**5 (15.2)**	**7 (21.2)**
Back pain	1 (3.3)	3 (9.1)	2 (6.1)
Muscle spasms	0	1 (3.0)	2 (6.1)
Myalgia	2 (6.7)	1 (3.0)	1 (3.0)
Infections and infestations	**6 (20.0)**	**7 (21.2)**	**3 (9.1)**
Nasopharyngitis	1 (3.3)	1 (3.0)	2 (6.1)
Bronchitis	0	2 (6.1)	0
Respiratory, thoracic and mediastinal disorders	**2 (6.7)**	**6 (18.2)**	**1 (3.0)**
Pharyngolaryngeal pain	1 (3.3)	3 (9.1)	0
Cough	0	2 (6.1)	0
Psychiatric disorders	**2 (6.7)**	**3 (9.1)**	**3 (9.1)**
Insomnia	1 (3.3)	2 (6.1)	1 (3.0)
Skin and subcutaneous tissue disorders	**3 (10.0)**	**4 (12.1)**	**0**
Pruritus	0	2 (6.1)	0
Erythema	2 (6.7)	0	0
Ear and labyrinth disorders	**0**	**1 (3.0)**	**2 (6.1)**
Vertigo	0	1 (3.0)	2 (6.1)

SAF: Patients who took at least 1 tablet of study medication as confirmed by returned medication.

Source: Table 12.6.1.2

Deaths, Other Serious Adverse Events and Adverse Events Resulting in Discontinuation

Attachment 1 contains narratives for patients who died, experienced other serious adverse events, and/or discontinued study/study drug due to an adverse event.

[redacted] occurred during the study. Patient [redacted] in the placebo group [redacted] on day 59 due to [redacted]. The investigator considered the [redacted] not related to study drug. [Appendix 13.2.7.3 and Attachment 1].

Other Serious Adverse Events

No SAE occurred during part 1. Two SAEs in addition to the fatal event occurred in study part 2 (both in placebo recipients):

Patient [redacted] with onset on day 4 that met the criteria for an SAE. The event was attributed a probable relationship to study drug and prompted the [redacted] from the study (see Adverse Events Resulting in Discontinuation). The [redacted] [Appendix 13.2.7.4, Appendix 13.2.7.5 and Attachment 1].

Patient [redacted] with onset on day 51. The event was considered not related to study drug but prompted [redacted] of study drug. The event was documented as resolved on day 85 [Appendix 13.2.7.4 and Attachment 1].

Adverse Events Resulting in Discontinuation

Four patients (2 in the placebo group and 1 each in the ASP9831 groups) experienced a TEAE that led to permanent discontinuation of the study [Table 12.6.1.1].

Patient [redacted] in the placebo group [redacted] on day 59 due to [redacted] [Appendix 13.2.7.5 and Attachment 1].

Patient [redacted] in the placebo group [redacted] as result of an SAE of [redacted] (described in Other Serious Adverse Events).

Patient [redacted] in the ASP9831 50-mg dose cohort experienced the only severe TEAE reported among all ASP9831 recipients. [redacted] with onset on day 3 and resolution on day 6 was attributed a possible relationship to study drug. Last dose was on day 4 [Appendix 13.2.7.5 and Attachment 1].

Patient [redacted] in the ASP9831 100-mg dose cohort experienced [redacted] with onset on day 1 that led to [redacted]. The event was attributed a probable relationship to study drug by the investigator [Appendix 13.2.7.5 and Attachment 1].

Subgroup Analysis of Treatment-emergent Adverse Events

Analysis of TEAEs according to age group (< 65 years, ≥ 65 years) [Table 12.6.1.11.1], sex (male, female) [Table 12.6.1.11.3], fibrosis stage (none, stages 1, 2, 3) [Table 12.6.1.11.5] and diabetes type 2 (yes, no) [Table 12.6.1.11.7] showed no obvious increased rate of any TEAEs associated with any subgroup. No definite differences could be determined considering the small sample size of some subgroups (e.g., only 1 patient in part 1 and 4 patients in part 2 were age 65 years or older; 2 patients in part 1 were female and the number of females in part 2 ranged from 5 in the placebo group to 8 and 9 in the 2 ASP9831 groups; 2 patients with fibrosis stage 1, 2 patients with fibrosis stage 2 and 6 patients with fibrosis stage 3 in part 1 and 3 to 12 in the fibrosis stage subgroups per treatment group in part 2).

Clinical Laboratory Evaluations

Quantitative summaries of clinical laboratory assessment results in part 1 showed no adverse changes in biochemical or hematological analytes over time. In study part 2, mean values of biochemical [Table 12.6.2.1.1] and hematological [Table 12.6.2.1.2] analytes over time represented small, mixed decreases and/or increases. Urine pH remained stable over time in all 3 groups [Table 12.6.2.1.4].

CONCLUSIONS:

Neither ASP9831 50 mg nor ASP9831 100 mg showed a significant decrease in ALT or in AST compared to placebo. ALT and AST values in the placebo control group remained stable over time.

ASP9831 had no effects on any of the biomarkers measured.

The non-compartmental pharmacokinetic analysis showed a dose proportional increase in C_{max} and AUC when the dose increased from 50 to 100 mg BID. No dose dependency was observed for $t_{1/2}$, CL/F and V_Z/F. Evaluation of pharmacokinetic data from patients with NASH in this study versus data from healthy volunteers (study 9831 CL-0001), showed the mean, as well as the median, t_{max} was about 2-fold longer and the mean C_{max} was approximately 2-fold lower in patients compared to healthy subjects.

Conclusions continued→

Conclusions – continued

Use of a pharmacokinetic model to describe plasma concentration curves of ASP9831 (part 1 and part 2) and to explore relationships between covariates and pharmacokinetic parameters indicated that weight and AST were covariates for clearance:

- clearance increased about 0.87 L/h for each 10 kg extra weight, and
- clearance decreased about 0.24 L/h for each 10 U/L extra AST.

No major differences between individual estimates for the pharmacokinetic parameters obtained by non-compartmental and population pharmacokinetic analysis were found. Differences found were attributable to the small number of subjects and the use of sparse sampling in part 2 of the study.

The dose-dependent incidence of TEAEs was evident in the occurrence of diarrhea and nausea, which are considered related to the mode of action of PDE4 inhibitors. Both ASP9831 treatment groups, 50 and 100 mg BID, showed a higher incidence of TEAEs compared to placebo. ASP9831 100 mg had a higher incidence than ASP9831 50 mg.

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