Novartis Clinical Trial Results

Name of finished product: N/A

Name of active ingredient: BAF312/Siponimod

Study number: CBAF312A2130

Title of study: A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the modulation of immune response to T-cell dependent and T-cell independent antigen stimuli by preceding, concomitant and interrupted administration of multiple therapeutic doses of BAF312 in healthy subjects

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Study center(s):

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Study period

First subject enrolled: 02-Dec-2013 Last subject completed: 26-Jan-2015

Phase of development: I

Objectives:

Primary: To compare the influence of preceding, concomitant and interrupted BAF312 administration on the efficacy of a T-cell dependent (influenza) and T-cell-independent (PPV-23) vaccination in healthy subjects relative to placebo.

Secondary: To assess the safety and tolerability of multiple, therapeutic doses of 2.0 mg/d BAF312 up to 38 days in healthy subjects.

Methodology: This was a Phase I, non-confirmatory, randomized, double-blind, placebo-controlled, parallel group study to evaluate the impact of BAF312 administration on immune response function after PPV-23 and influenza vaccination.

The study consisted of a 28-day screening period, a 48-day treatment period followed by a 14-day follow-up period. Each subject underwent vaccination challenge on Day 21 along with a baseline immunoglobulin (Ig) assessment in the same morning followed by weekly antigen-specific antibody determinations until four weeks post challenge (Day 49). An additional antibody assessment was done on Day 63. A Study Completion evaluation was done within one to three weeks after last immunoglobulin determination (Day 70-84).

The study subjects were equally randomized into 4 groups (n=30 per group). Group 1 evaluated the impact of interrupted BAF312 treatment on immune response function. The subjects (n=30) received 10 days of BAF312 followed by

placebo, vaccination challenge on Day 21, again placebo for 14 days, and finally 14 days of BAF312.

Group 2 evaluated the impact of preceding BAF312 regimen. The subjects (n=30) received BAF312 for 13 days followed by 7-days of placebo, then a vaccination challenge on Day 21 again followed by placebo for 28 days.

Group 3 assessed the impact of concomitant BAF312 administration. Starting with placebo for 10 days, the subjects received BAF312 for the next 38 days with a in between vaccination challenge on Day 21.

Group 4 subjects were administered placebo for 48 days with a vaccination challenge on Day 21. All the groups received BAF312 administration in a 5-day up-titration regimen.

Number of subjects (planned and analyzed): 120 (planned); 136 (enrolled and analyzed)

Main criteria for inclusion:

Main inclusion criteria

Healthy male and female subjects aged 18 to 55 years weighing at least 50 kg and with a body mass index (BMI) within 18.0-30.0 kg/m^2 were included in this study. The female subjects were required to be of non-child bearing potential.

Main exclusion criteria

Subjects with the CYP2C9 *3/*3 genotype and subjects who had previously undergone any vaccination with PPV-23 (Pneumovax) or any type of influenza vaccine were not included in the study. Subjects having history or presence of any clinically significant disease of any major system organ class including (but not limited to) cardiovascular, metabolic, renal, neurological or psychiatric diseases which has not resolved within two weeks prior to initial dosing; or any clinically significant ECG abnormalities; hypersensitivity to BAF312 or to any other S1P receptor modulator; any malignancy of any organ system treated or untreated, within the past 5 years prior screening, were also excluded. Pregnant or nursing women and subjects who smoked were excluded. Subjects with any abnormalities of laboratory values that were considered as clinically significant per investigator's judgment were excluded from the study.

Test product, dose and mode of administration: The BAF312 tablets were supplied to the investigator sites at dose strengths of 0.25 mg, 0.5 mg, 1 mg, 2 mg and 0 mg (matching placebo) as open labeled bulk medication. The Pneumovax® and inactivated influenza vaccine Fluvirin® were sourced by Novartis.

The subjects received oral 2 mg dose of BAF312 following a 5-day up-titration period (Days 1and 2: 0.25 mg; Day 3: 0.5 mg; Day 4: 0.75 mg; Day 5: 1.25 mg, followed by 2 mg on subsequent days).

Duration of treatment: The study consisted of a 28-day screening period, a 48-day treatment period followed by a 14-day follow-up period. Each subject

underwent vaccination challenge on Day 21. Subjects were exposed to BAF312 dosing for a minimum of 10 days to achieve pharmacokinetic (PK) and pharmacodynamic (PD) steady-state conditions.

Reference therapy, dose and mode of administration, batch number: Group 4 subjects were administered placebo for 48 days with a vaccination challenge on Day 21.

Criteria for evaluation

Efficacy/ pharmacodynamics: A 5 ml serum sample for the measurement of Influenza-specific and PPV-23-specific antibody determinations was collected on Study day 21, 28, 35, 42, 49 and 63.

Pharmacodynamic assessments included the determination of antibody concentrations or titers at baseline (i.e., just prior antigen challenge) as well as 7, 14, 21, 28, and 42 days after antigen challenge
i.e. single intramuscular (IM) injection of PPV-23 and influenza vaccine.

Efficacy of the vaccines was determined based on antibody titers obtained at four weeks after antigen challenge according to the following definitions:

- Influenza: Response was defined by a > 4-fold increase of antihaemagglutinin antibody titers at four weeks after vaccination compared to baseline
- PPV-23: > 2-fold increase of IgG concentrations at four weeks after vaccination compared to baseline

In terms of PPV-23, IgM concentrations were also determined to better characterize the time course of the antibody response.

Safety: Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at (study center/central laboratory) and regular assessments of vital signs, physical condition, height and weight, and ECG (single 12-lead ECG and online cardiac monitoring from 1 hour pre-dose to at least 6h post each dosing).

Prospective suicidality (suicidal ideation and suicidal behavior) was assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS).

Pharmacokinetics: BAF312 pre-dose PK blood samples were collected on days 3, 6, 8, 10, 13, 16, 18, 21, 28, 37, 40, 42, and 45 within 60 min prior to dosing. BAF312 post-dose PK samples were collected on Days 49 and 63.

Statistical methods:

Analysis of primary variable

The primary aim of this study was to compare the efficacy of a T-cell dependent influenza and T-cell- independent PPV-23 vaccination in healthy subjects as influenced by interrupted, preceding, or concomitant BAF312 treatment against placebo.

The primary outcome variable was the response to a vaccination induced by PPV-23 and influenza vaccine. Response was defined by a > 4-fold increase of anti-hemagglutinin-inhibition titers for influenza vaccine and > 2-fold increase of IgG concentration for PPV-23 vaccine at four weeks after vaccination compared to baseline. Thus, the response was a binary data with 1 stands for meeting the definition and 0 for failing to meet the definition. The primary variable was analyzed per protocol (i.e. was analyzed under the actual treatment group).

Analysis of secondary variables

- Safety: All information obtained on AEs was displayed by treatment and subject. The number and percentage of subjects with adverse events were tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple AEs within a body system was only counted once towards the total of this body system.
- All vital signs data were listed by treatment, subject, and visit/time and if ranges were available abnormalities (and relevant orthostatic changes) were flagged. All ECG data were listed by treatment, subject and visit/time, abnormalities were flagged. All laboratory data were listed by treatment, subject, and visit/time and if normal ranges were available abnormalities were flagged. Summary statistics was provided by treatment and visit/time.
- Pharmacokinetics: BAF312 plasma concentration data was listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics was provided by treatment and visit/sampling time point. Summary statistics included mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ were treated as zero in summary statistics. A geometric mean was not reported if the dataset included zero values.

Summary - Conclusions

Demographic and background characteristics: There were 106 males and 30 females enrolled and dosed in this study. The mean age of the subjects was 36.6 years (range: 18-55) and mean weight 77.3 kg (range 56.1 - 101.3 kg). Demographic data did not show any major differences between treatment groups.

Pharmacodynamic results:

Influenza (T-cell dependent)

- Response was defined by ≥4-fold titer increase of Anti-hemagglutine inhibition titers at four weeks post vaccination compared to baseline
- Non-inferior responder rates with respect to each of the four antigens were determined for the preceding treatment group, but not for the interrupted and concomitant treatment group. PPV-23 (T-cell independent)
- Response was defined by ≥2-fold increase of IgG concentrations at four weeks post vaccination compared to baseline.
- Non-inferior responder rates determined in all BAF312 treatment groups compared to placebo.

Pharmacokinetic results:

- BAF312 pre-dose concentrations indicated that the subjects were adequately exposed in each of the three BAF312 treatment groups
- Steady state plasma concentrations were comparable to historical observations and in most subjects achieved at 2 mg q.d. as expected after approximately 10 days of treatment.

Safety results:

- The overall incidence of adverse events was similar in the BAF312 treatment groups as in the placebo group (35.3-55.9% vs. 38.3%)
- The most commonly reported system organ class were nervous system disorders with headache representing the most common individual AE
- Most AEs were of mild intensity, had an early onset and spontaneously resolved within less than 24 hours
- There were only two subjects with AEs leading to individual discontinuation.
- There were no clinically relevant findings of laboratory, vital sign or ECG data noted. These data was similar across treatment groups or there were no marked trends over time.
- In this study, BAF312 was safe and tolerated at a dose of 2mg q.d. in healthy subjects.

Conclusion:

Non-inferior responder rates were identified for the T-cell independent vaccination with PPV-23 with respect to each of the three BAF312 treatment groups. Hence, BAF312 treatment even when given concomitantly at a therapeutic multiple dose of 2 mg qd is not considered to compromise the efficacy of PPV-23 vaccination as defined in the context of this study.

In terms of influenza, non-inferior responder rates have been determined with respect to the preceding treatment group. Hence, efficacy of an influenza vaccination as defined in the context of this study is not considered to be compromised in case BAF312 treatment is paused one week prior until four weeks after an influenza vaccination. Even though non-inferiority has not been established with respect to the interrupted and concomitant treatment group, there was also a reasonable titer increase noted in both groups and responder rates were only approximately 15%-30% lower than on placebo.

Date of report: 25-Jun-2015

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230

Swissmedic Approval Date: 22-Oct-2020

Novartis Study Code

CBAF312A2130

EudraCT Number

Not applicable.

Planned and Actual Number of Patients

Planned: 120 subjects

Enrolled: 136 subjects

Batch Numbers

Study drug and strength	Formulation control number	Batch number
BAF312 0.25 mg	PCN 13-0312CH	13-0312CH/X274 1111
	PCN 14-2383CH	14-2383CH/X002 0113
BAF312 0.5 mg	PCN 13-0312CH	13-0312CH/X275 1111
	PCN 14-2383CH	14-2383CH/X004 0113
BAF312 1 mg	PCN 13-0312CH	13-0312CH/X273 1111
	PCN 14-2383CH	14-2383CH/X005 0113
BAF312 2 mg	PCN 13-0312CH	13-0312CH/X276 1111
	PCN 14-2383CH	14-2383CH/X008 0113
Pneumovax®	NDC 0006-4943-00	K004281
Influenza vaccine	NDC 66521-117-02	145202

Information on comparators drug dosage, route of administration, batch numbers

Study drug and strength	Formulation control number	Batch number
Placebo	PCN 13-0312CH	13-0312CH/X007 0112

Publication(s)

Ufer M, Shakeri-Nejad K, Gardin A, Su Z, Paule I, Marbury TC, Legangneux E. Effects of siponimod on vaccination-induced immune response: A randomized, double-blind study. Neurol Neuroimmunol Neuroinflamm. 2017 Nov; 4(6): e398. ePub13 Sep 2017. Doi: 10.1212/NXI.0000000000000398.

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