A Phase I Dose Escalation Study to Investigate Safety, Tolerability, and Pharmacokinetics of ANAVEX 2-73 in Healthy Male Subjects

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Background

• Cognition enhancing both symptomatic and disease modifying R&D programs are still important to Alzheimer’s disease
• ANAVEX 2-73 (AV2-73) combines muscarinic pharmacology with sigma-1 agonism and can potentially combine symptomatic with neuroprotective and disease modifying properties (Villard 2011, Lahmy 2013)

Study design

A randomized, double-blind, placebo-controlled within each dosage step, two cohorts alternating single dose escalating study in male healthy subjects.

Study Period

First subject enrolled: 11-APR-2011
Last subject completed: 14-NOV-2011

Objectives

Primary
To evaluate the safety and tolerability of AV2-73 following single oral administration of escalating doses in male healthy subjects.

Secondary
To determine the pharmacokinetics of single oral doses of AV2-73.

Subjects

16 subjects divided into 2 cohorts of 8 subjects: Cohort A (n=8) and Cohort B (n=8), replacement of drop out subjects for following dose steps (total: 22 subjects)
Main criteria for inclusion: Healthy male Caucasian subjects between 18 and 55 years

Treatments

Study medication consisted of capsules containing 1, 10 or 50 mg AV2-73 and corresponding placebos. Capsules were administered under fasting conditions with 200 ml of still mineral water. The table below shows all single doses that were administered:

Dose
1
10
50

Procedures from Day 1 to Day 3:
On Day 1 subject randomization, administration of trial medication starting at around 8:00 am, repeated blood sampling for AV2-73 and metabolite AV19-144 plasma concentration determination from T0 (before IMP administration) to T+48h, urine sample collection for determination of AV2-73 and AV19-144 between 4h-4h, 8h-8h, 24h-48h p.a., physical examination at 48 hours post-dose, safety laboratory, continuous cardio-respiratory monitoring via telemetry from pre-dose to over 4 hours post-dose; repeated 12/lead safety ECG recordings from T0/pre-dose (3 baseline ECGs) to T+48h, vital signs measurements (heart rate, SBP and DBP, respiratory rate, oxygen saturation [pulse oximetry], body temperature [BT]) from T0/pre-dose to T+48h, adverse events recording.

Subjects were discharged from the study ward in the morning of Day 3 (ca. 48 h post dosing).

Dishing Visit (study follow-up visit) on Day 7 after last dosing physical examination, weight, blood pressure, body surface area, laboratory safety ECG, vital signs (heart rate, SBP and DBP, respiratory rate, oxygen saturation [pulse oximetry], body temperature), urine drug screen and alcohol test, adverse events recording, concomitant medications and medical procedures recording.

Subjects showing either subjective or objective abnormalities at the completion of the study were to be followed up until the condition resolved or an adequate explanation was found.

Bioanalysis

AV2-73 and metabolite AV19-144 were determined in plasma and urine using a validated high performance liquid chromatographic method (HPLC) with tandem mass spectrometry. After separation from human plasma samples, analytes were injected into a LC-MS/MS. Quantification in plasma and urine was conducted by an internal standard method (AV2-73) and a peak area ratio method (AV19-144). A weighted (1/x) regression 2nd order was used to determine the concentration of the analytes. The study was conducted in accordance with the Principles of Good Laboratory Practice (GLP) as described under § 19, German Chemical Law. The validation based on the EUG-Dok. CPM/ICH/C8/95 and was reported according to “FDA-Guidance for Industry, Bianalytical Method Validation” (May 2001).

Criteria for Evaluation

Safety Parameters:
adverse events (AE), 12-lead ECG and vital signs, physical examination, laboratory tests (haematology, plasma biochemistry, urinalysis).

Pharmacokinetics:
blood samples for AV2-73 and metabolite plasma concentration, urine samples for AV2-73 and metabolite urine concentration

Statistical methods

Safety analysis: primary objective was the safety and tolerability of study medication. The primary analysis included: rate of subjects having experienced at least one AE, Absolute and relative frequency of subjects having experienced at least one AE were calculated by group of treatment period. Total number of AEs: absolute frequency of AEs were calculated by group of treatment period.

descriptive statistics on each further safety parameter (such as vital signs, ECGs, and laboratory tests) were conducted. Phamacokinetic analysis: descriptive statistics on each parameter (such as Cmax, t1/2, AUC(0-t), AUC(0-∞)) was calculated by dose.

Results

Safety and Tolerability: Adverse events (AEs): 13 of 22 subjects (incident 59.1%) experienced a total of 41 AEs. No serious adverse event was reported. There was no study discontinuation due to AEs. One (1) of the 41 AEs [2.4%] (headache) had its onset before dosing, thus it was only non-treatment-emergent adverse event (non-TEAE). Most AEs (32) were of mild intensity (32/41 = 78.0%). The remaining nine (9) AEs were rated as moderate intensity (9/41 = 22.0%). Most TEAEs (31/41 = 77.5%) were of mild intensity. The remaining 9 TEAEs had moderate intensity and exclusively occurred at the highest dose levels 55 and 60 mg.

Dizziness was the most frequent AE (incidence: 11/41 = 26.8%). 8 episodes of dizziness were of mild intensity, the remaining 3 were of moderate intensity. All 11 cases of dizziness were reported by the AV2-73 administered subjects. The number of affected subjects increased with increasing dose from 2 of 6 (25%) subjects to 4 of 4 subjects (100%) at the 30 mg and 60 mg dose steps, respectively. Headache was the second most common AE (7/41 = 17.0%).

Gastrointestinal effects were predominantly observed at the highest 60 mg dose. The complaints were abdominal pain (1), nausea (2), vomiting (3), and loose stools (1). Other side effects observed were one subject experienced euphoric mood and one subject presented with mild depressant symptoms, each at the highest dose levels.

In summary, there was a clear trend for dose dependence of both frequency and intensity of TEAEs across the AV2-73 dose levels from 1 to 60 mg. Three out of four subjects at 60 mg experienced total 6 dose limiting TEAEs.

Vital signs: There were no dose related differences of BP, and resting HR. Analysis of ECGs did not reveal any dose-related or time-dependent changes for any of the hematology, biochemistry, and coagulation parameters could be detected.

Urinalysis: A number of marginal, clinically not significant out of normal results were observed throughout the entire study across all dose groups. No sign for any dose- or time-dependent changes for any of the tested urinalysis parameters could be detected.

Pharmacokinetics:

ANAVEX-273: The mean of maximum plasma concentration (Cmax) values of AV2-73 showed a dose dependent increase with exception of the 60 mg dose step.

The mean values of area under the plasma concentration-time curves from zero to last quantifiable point and to infinity (AUC(0-∞)) demonstrated a dose proportional linear increase.

The mean time to maximum plasma concentration (tmax) values across all dose groups were about 1 to 2 h, with no tendency of dose dependence.

ANAVEX-1914-144: The mean plasma Cmax values of the metabolite AV19-144 were lower than that of the parent compound and showed a dose proportional linear increase over the dosage range from 10 to 60 mg.

The mean values of AUC(0-∞) and AUC(0-t) over the dosage range from 30 to 60 mg were significantly higher than that of AV-73 and showed a dose proportional linear increase.

The T1/2 values of AV2-73 across all dose groups ranged from 2.5 to 3.9 h, with no tendency of dose dependence.

Conclusions

• Ascending single oral doses of 1 mg, 10 mg, 30 mg, 40 mg, 50 mg and 55 mg of AV2-73 were safe and well tolerated in healthy male subjects.

• Dizziness was the most frequent adverse event.

• There was a clear trend for dose dependence of both frequency and intensity of TEAEs across the AV2-73 dose levels from 1 to 60 mg. Three out of four subjects at 60 mg experienced total 6 dose limiting TEAEs.

• Clinical laboratory parameters, vital signs, and 12-lead ECG evaluation did not show any clinically relevant or dose dependent changes.

• Based on frequency and intensity of TEAEs the maximum tolerable dose (MTD) and the minimum intolerable dose (MID) were defined as 35 mg and 60 mg, respectively.

• The pharmacokinetic data reveal a rapid and extensive biotransformation of AV2-73 to its main metabolite AV19-144 after oral administration.

• Linear pharmacokinetics after single oral dosing of 1 mg up to 60 mg AV2-73 can be assumed.

• The results of the study demonstrate that the design was suitable both to define MTD and MID of AV-273 and to describe pharmacokinetics after administration of single oral doses from 1 to 60 mg.

References

• Lahmy, Neuropsychopharmacol (2013), pp. 1700-1723