EVT 201: First Phase II Results
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EVT 201: Pharmacological Profile

- EVT 201 is a high affinity, alpha-1 preferring partial positive allosteric modulator (pPAM) of $GABA_A$ receptors
- As a pPAM, EVT 201 produces a lower maximal potentiation of $GABA_A$ receptors than a full agonist
- EVT 201 has a half-life of 3 to 4 hours in young and elderly giving it ideal pharmacokinetic properties without the need for a sustained release formulation

EVT 201: Clinical Development Summary

Study BP15911 (Roche)
Single ascending dose study 0.3 mg – 20 mg
65 subjects (39 active)

Study EVT-2001
Dose finding 2.5 mg – 10 mg
Road Traffic Model of Insomnia
12 subjects (healthy male volunteers)

Study EVT-2002
Dose finding 1 mg – 2.5 mg
Road Traffic Model of Insomnia
12 subjects (healthy male volunteers)

Study EVT-2003-1
Single ascending dose in elderly 1, 2, 2.5 mg
24 subjects

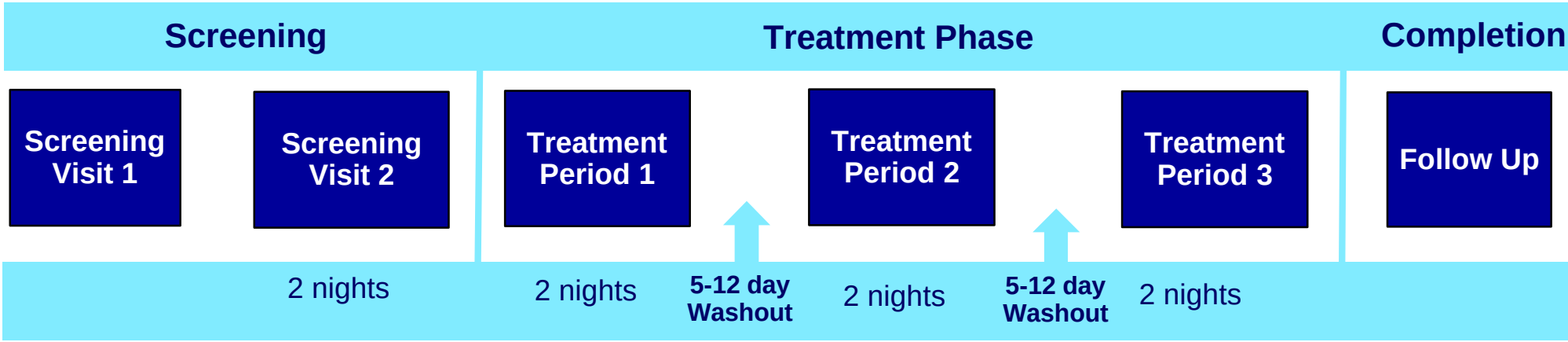
Study EVT-2003-2
Repeat dose in young
1.5 & 2.5 mg
24 subjects

Study EVT-2003-3
Repeat dose in elderly
2.5 mg
16 subjects

Study EVT-2004
Phase II proof-of-concept
1.5 mg & 2.5 mg doses primary insomnia patients
Cross-over study in 67 completed patients

Study EVT-2005
Phase II elderly patients
1.5 mg & 2.5 mg doses elderly primary insomnia patients
Parallel group study in 135 patients

EVT 201 Study 2004 : Study Design



- A randomized, multicentre, double-blind, placebo-controlled cross-over study to assess the efficacy of two doses of EVT 201 (1.5 mg, 2.5 mg)
- Each treatment was administered for two nights with a 5-12 day washout between each treatment period
- Dosing 30 minutes before lights out
- PSG for 8 hours from lights out on nights 1 and 2 of each treatment period
- Centralised PSG scoring

EVT 201 Study 2004: Key Eligibility Criteria

- Documented diagnosis of primary insomnia (DSM-IV criteria)
- Aged < 65 years
- On screening PSG 2 nights with:
  - LPS > 20 min (no night <15 min)
  - Mean WASO = 40 min
  - Mean TST 240-420 min inclusive

  - Study powered for an increase in TST of 20 mins and a decrease in WASO of 15 mins at 80% power

EVT 201 Study 2004: Endpoints

PSG derived co-primary endpoints:

- Total Sleep Time and Wake After Sleep Onset

Secondary endpoints include:

- Latency to Persistent Sleep (LPS)
- Sleep architecture
- Patient reported sleep variables
- Categorical rating by the patient for sleep quality
- Residual sedation measures (assessed 30 ± 10 minutes after lights-on) including:
  - Categorical rating by the patient
  - Digit Symbol Substitution Test (DSST)
- Safety endpoints

EVT 201 Study 2004: Top-Line Efficacy Results

EVT 201 has robust effects on both sleep onset and sleep maintenance.

- Results from 67 patients - intention to treat (ITT) analysis

Parameter	1.5mg vs placebo	2.5mg vs placebo
Adjusted mean TST (mins)	p<0.001	p<0.001
Adjusted mean WASO (mins)	p<0.001	p<0.001
Adjusted mean LPS (mins)	p<0.001	p<0.001
Adjusted mean total wake time, 2nd half (mins)	p<0.001	p<0.001

EVT 201 Study 2004: Top-Line Results

Secondary endpoints

- Patients reported highly significant improvements in subjectively assessed quality of sleep ($p<0.001$ both doses)
- No effect on subjectively assessed residual sedation the next day
- A small decremental effect on the digital symbol substitution test (DSST) assessed at nine hours post dose
- No impairment of Slow Wave Sleep (SWS)

Analysis of other secondary endpoints is ongoing.

EVT 201 Study 2004: Safety Results

- Low incidence of adverse events
- No serious adverse events reported
- EVT 201 was safe and well tolerated

EVT 201 Study 2005: Status

Study 2005

A second Phase II efficacy study in elderly primary insomnia patients with daytime sleepiness is ongoing in the US

Planned number of subjects

135

Recruitment status

- Just under two thirds of the patients have been enrolled
- The study is on track for reporting top-line results Q4 2007 / Q1 2008

EVT 201: Conclusions

- Proof-of-Concept for EVT 201 has been demonstrated in patients
- These robust data support the potential of EVT 201 to induce sleep and maintain sleep without next-day residual effects
- Evotec has thereby delivered on its stated strategy
- A key piece of the data package for partnering EVT 201 is now in place