Otsuka collaborations (brexpiprazole and Lu AE58054)

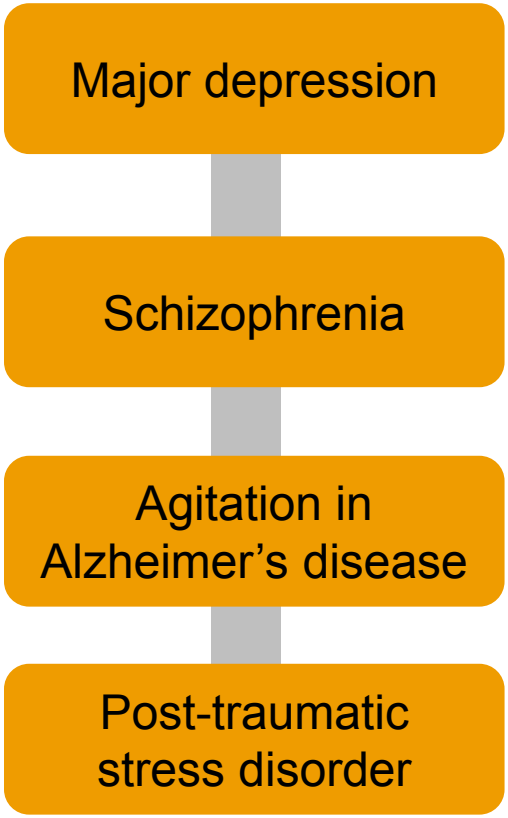
Despite progress and wide range of available therapies, no current therapy addresses all needs

UNMET NEEDS IN DEPRESSION

- Inadequate treatment response in many patients, despite treatment switches[1]
- Cognitive symptoms in depressed patients are not adequately treated with current antidepressants[2-4]
- Nausea, sexual dysfunction, insomnia and weight gain are common tolerability issues with e.g. SSRIs and SNRIs[5-8]

1. Rush AJ et al. 2006; 2. Uher R *et al.* 2012; 3. Wihall A *et al.* 2009; 4. Jaeger J *et al.* 2006; 5. Bull 2002; 6. Kelly 2008; 7. Cassano 2004; 8. Masand 2003

Brexpiprazole represents a substantial promise and rationale



- Favourable tolerability profile vs. other anti-psychotics
- Synergistic effect with SSRIs/SNRIs
- Positive outcome[1)] from first out of two studies (EPA) – read-out from second trial in H1 2014

- Broad efficacy profile
- Favourable tolerability profile vs. other anti-psychotics
- Read-out from two phase III studies in H1 2014

- Two phase III studies with ~800 patients (≤2mg)
- Read-out from phase III expected in 2017

- A phase III study with ~600 patients (≤3mg)
- Read-out from phase III expected in 2015

1) M.E. Thase et al: " *Efficacy and safety of adjunctive brexpiprazole ((OPC-34712) in major depressive disorder (MDD): A phase III, randomized, placebo-controlled study"; EPA 2004 (abstract)*

Brexpiprazole – a new treatment for a range of psychiatric disorders

Brexpiprazole phase II (study no. 211)

- Effective as adjunctive treatment in MDD patients with inadequate response to prior antidepressant therapy
- Statistically significant reductions in MADRS total score as early as week 2 after initiation of treatment with brexpiprazole

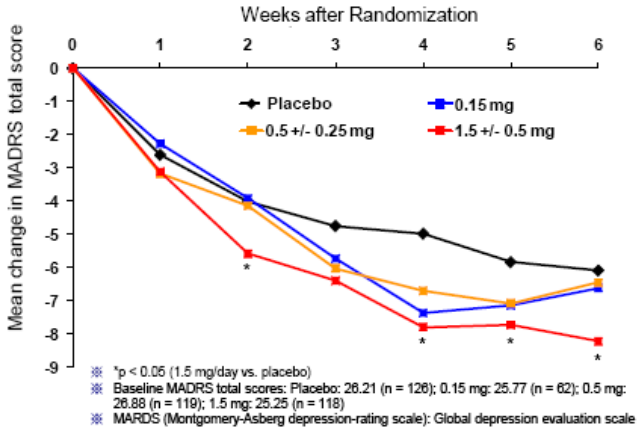
Development status

- Schizophrenia: Five phase III studies recruiting
- Major depression adjunctive therapy: Nine phase III studies recruiting
- Alzheimer's/dementia: Two studies recruiting
- PSTD: One study recruiting

Mechanism of action

- Novel D_2/D_3 receptor partial agonist
- 5-HT_{1A} partial agonist
- 5-HT_{2A} antagonist

Phase-IIb OPC-34712 efficacy results (study no. 211): Change in MADRS total score



* $p < 0.05$ (1.5 mg/day vs. placebo)
* Baseline MADRS total scores: Placebo: 26.21 (n = 126); 0.15 mg: 25.77 (n = 62); 0.5 mg: 26.88 (n = 119); 1.5 mg: 25.25 (n = 118)
* MARDS (Montgomery-Asberg depression-rating scale): Global depression evaluation scale

Clinical programme with brexpiprazole - adjunctive therapy in MDD plus "other indications"

Clinicaltrials.gov identifier	Estimated enrolment	Study start	Indication
NCT01727726 (phase III)	1,340 (US)	Dec 2012	Adjunctive therapy in MDD (Delphinus) - flexible-dose. Brexpiprazole+ADT; placebo+ADT; seroquel+ADT, endpoint: MADRS score
NCT01360866 (phase III)	1,209 (US)	Oct 2011	*ORION:* Adjunctive therapy in MDD. 0.5-3 mg brexpiprazole+ADT, endpoint: adverse events
NCT01360645 (phase III)	925 (US)	Jul 2011	*PYXIS:* Adjunctive therapy in MDD. 2mg brexpiprazole+ADT; placebo+ADT, endpoint: MADRS score
NCT01360632 (phase III)	1,650 (US)	Jun 2011	*POLARIS:* Adjunctive therapy in MDD. 1+3mg brexpiprazole+ADT; placebo+ADT, endpoint: MADRS score
NCT01838681 (phase III)	1,462 (EU)	May 2013	1-3mg. Inadequate responders in MDD; Up to 36 wks
NCT01837797 (phase III)	1,334 (elderly)	April 2013	1-3mg. Up to 20wks
NCT01447576 (phase II)	1,038 (US)	Sep 2009	Adjunctive therapy in MDD. 1-3mg brexpiprazole+ADT, endpoint: adverse events
NCT00797966 (phase II) [1)]	850 (US)	May 2009	Adjunctive therapy in MDD. 1-4mg brexpiprazole+ADT; placebo+ADT, endpoint: depression rating scale
NCT01052077(phase II)	773 (US)	Mar 2010	Adjunctive therapy in MDD (STEP-D222). 1-3mg brexpiprazole+ADT; placebo+ADT, endpoint: depression rating scale

*ST=stimulant therapy, ADT=FDA approved antidepressant treatment, 1) Published at APA 2011. Data presented at EPA, March 2014.

"Other indications"

Clinicaltrials.gov identifier	Estimated Enrolment	Study start	Indication
NCT01074294 (phase II)	675 (US)	Mar 2010	Complementary treatment in ADHD. 0.25+1mg brexpiprazole+ST; placebo+ST, endpoint: efficacy/safety
NCT01862640	560 (Global)	May 2013	Agitation Associated With Dementia of the Alzheimer's Type, 2-week, placebo, 3 Fixed Doses of Brexpiprazole (0.5mg, 1mg and 2mg)
NCT01922258	230 (Global)	Sep 2013	Agitation Associated With Dementia of the Alzheimer's Type, 12-week, placebo, 0.5-2mg
NCT01987960	592 (US)	Dec 2013	Brexpiprazole as Adjunctive Treatment to Paroxetine or Sertraline in Adult Patients Suffering From Post-traumatic Stress Disorder (PTSD), 28 wks, placebo, up to 3mg/day

Clinical programme with brexpiprazole - schizophrenia

Clinicaltrials.gov identifier	Estimated enrolment	Study start	Indication
NCT01810380 (phase III)	465	March 2013	To determine the efficacy and safety of brexpiprazole for the treatment of adults experiencing an acute episode of schizophrenia. Active ref: Seroquel
NCT01810783 (phase III)	140	May 2013	<4mg Safety and tolerability in schizophrenia. PANSS is secondary end-point. Up to 52 wks
NCT01668797 (phase III)	420 (US)	Oct 2012	Maintenance treatment of schizophrenia (Equator). 1-4mg brexpiprazole; placebo, endpoint: relapse
NCT01397786 (phase III)	1,000 (global)	Sep 2011	*ZENITH:* Maintenance treatment of schizophrenia. 1-2mg, 1-4mg brexpiprazole, Endpoint: adverse events
NCT01393613 (phase III)	660 (global)	Jul 2011	*BEACON:* Acute schizophrenia. brexpiprazole (low/medium/high dose), placebo, end point: PANSS score
NCT01396421 (phase III)	630 (global)	Jul 2011	*VECTOR:* Acute schizophrenia. brexpiprazole (low/medium/high dose), placebo, end point: PANSS score
NCT01456897 (phase III)	Na. (Japan)	Oct 2011	Long-term trial in schizophrenia.
NCT00905307 (phase II) [1)]	450 (US)	Jul 2009 (completed)	Acute schizophrenia. 4 diff. doses (0.25-6mg) of brexpiprazole (STEP 203); aripiprazole; placebo, dose establishing study
NCT01451164 (phase II/III)	N/A (Japan)	Oct 2011	Dose-finding trial in patients with schizophrenia. brexpiprazole (low/medium/high dose), placebo, end point: PANSS score

1) Published at 24th Annual US Psychiatric and Mental Health Congress,7-11 November 2011, Las Vegas, NV, USA