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CPP-115: The Next Generation GABA-AT Inhibitor

2012 Epilepsy Pipeline Update Conference

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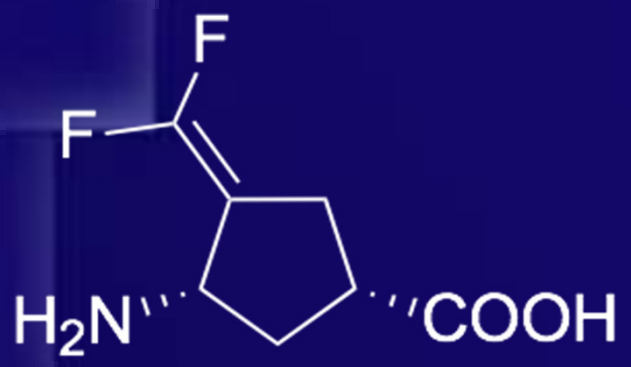

CPP-115 Value Proposition

- Next-generation GABA aminotransferase (GABA-AT) inhibitor
  - Orally delivered small molecule with ideal pharmacokinetics
- Same mechanism of action as vigabatrin, with improvements
  - Superior efficacy in an infantile spasms model
  - Improved visual safety, potency and specificity
- Targeted indications include cocaine dependency, infantile spasms and refractory complex partial seizures, among others in CNS
- Patent protection to 2028 with term extensions (new molecular entity)
- FDA fast track status for cocaine dependency
- Orphan drug status for Infantile Spasms (U.S.)
- Phase I data expected in Q2 2012
- Agreed-to development plan with FDA through Phase II

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Infantile Spasms Screening

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- "Multiple-Hit Model" for ACTH-refractory infantile spasms (Albert Einstein College of Medicine)
  - CPP-115 (0.1-1 mg/kg/day i.p.) suppressed spasms at doses 100-fold lower than vigabatrin, with better tolerance than vigabatrin[1]
  - CPP-115 more effective than vigabatrin in amount of seizure reduction and duration of action
    - Effective 3 days versus 1 day for vigabatrin
      - In this model, a few days is equivalent to months for a baby
    - No sedation in contrast to vigabatrin, which results in severe sedation when treating this condition

[1] Briggs SW, Ono T, Moshé SL, Galanopoulou AS (2011): presented at the American Epilepsy Society Meeting (December 2011)

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CPP-115 Anticonvulsant Screen

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Model	CPP-115[1][2]	Vigabatrin[1]
6 Hz Minimal Clonic Seizure (mouse, 32 mA, 3 seconds)	ED_{50}=5.2 mg/kg	ED_{50}=23.4 mg/kg
6 Hz Minimal Clonic Seizure (mouse, 44 mA, 3 seconds)	ED_{50}=28.4 mg/kg	ED_{50}=153.5 mg/kg
Corneal Kindling (8 mA, 60 Hz, 3 s, to stage 5 seizures)	ED_{50}=20.1 mg/kg	ED_{50}=80.4 mg/kg
Maximal Electroshock (60 Hz, 50 mA, 0.2 s, corneal electrode)	ED_{50}=58.9 mg/kg	ED_{50}>1000 mg/kg
Subcutaneous Picrotoxin, 2.5 mg/kg	ED_{50}=60.7 mg/kg	Not Available

[1] Time to peak effect was generally about 4 hours for both drugs, except for the scPIC model, which was 2 hours
[2] CPP-115 generally caused sedation related side effects above 60 mg/kg, However, toxic (sedative) effects were seen in the MES model below ED_{50}

- CPP-115 is similarly effective as vigabatrin in animal models, but is more potent
  - Where vigabatrin is effective, CPP-115 is also effective but at 4-5 times the potency
  - CPP-115 and vigabatrin are about equally ineffective in some other models
- CPP-115 causes sedation at a lower dose relative to its effective dose
  - Similar to vigabatrin, an initial dose titration will be needed to manage somnolence, and the sedating side effect will resolve in ~2-3 weeks
- Data provided by NIH's Anticonvulsant Screening Program

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CPP-115 Safety / Pharmacology

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- Minimal likelihood of drug-drug interaction
  - No inhibition of 8 common CYP enzymes and no induction of 4 common inducible CYP enzymes
  - Not metabolized
- Excellent pharmacological target specificity
  - No binding to 111 common pharmacological targets, all types of GABA receptors or transporters, or AST, ALT and SSADH
- No inhibition of hERG channels and no cardiovascular effects
- No respiratory effects
- Minimal likelihood of carcinogenicity
  - No observations of mutations in AMES test or chromosomal aberrations
- Favorable pharmacokinetics
  - Rapidly and completely orally absorbed and rapidly eliminated
  - Pharmacokinetics in people similar to vigabatrin

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CPP-115 Vision Study

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- Three arm study in Wistar rats: CPP-115, vigabatrin (positive control), saline (negative control)

	Effective Dose (Rats)	Vision Study Dose	Vision Safety Margin	45 Day Retinal Function Loss (ERG)	90 Day Retinal Function Loss (ERG)
Vigabatrin	300 mg/kg	200 mg/kg	~1	~30-60%	~45-60%
CPP-115	< 1 mg/kg[1]	20 mg/kg	> 20	~5-30%	~10-35%

[1] For infantile spasms in Multiple Hit Model, and dose shown to inhibit GABA-AT

- Retinal histology testing confirms ERG results and differences
- CPP-115, at 20 times its effective dose, is safer than vigabatrin at its effective dose
- CPP-115, at its effective dose, will likely be even safer
  - Potentially no Visual Field Defect (VFD) risk

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