pharmaceuticals

ADDITIONAL DUE DILIGENCE MATERIALS
IP OVERVIEW

OCTOBER 2017

OVERVIEW OF INTELLECTUAL PROPERTY

- We are developing LB-102 and LB-103: novel derivatives of amisulpride with the addition of a methyl group
- Provisional patent application (62/427062) filed November 2016 and amended May 2017 (62/508263), covers composition of matter.
  - LB will file PCT application on or before November 28, 2017. National phase filing deadlines (US, EU, South Korea, China, etc..) will be between May and July 2019
  - Future data may expand and increase duration of IP
- Benefits of LB-102/103 over amisulpride
  - *In vitro* data suggests that LB-102/103 significantly improves permeability of drug into the brain
  - *In vivo* data shows that LB-102 and LB-103 are efficacious in three models (two species) of positive and negative symptoms of schizophrenia
    - LB-102 showed statistically significant improvement over amisulpride in a Locomotor Activity model in rats
    - LB-102 was equivalent to amisulpride in a Novel Object Recognition model in rats and an Induced Climbing study in mice
    - No difference in a model of catalepsy between LB-102 and amisulpride
  - *In vivo* data suggests that LB-102/103 demethylates 50% into amisulpride (consistent in both rats and mice); receptor occupancy data suggests that both molecules act as effective anti-psychotics
  - If LB-102/103 delivers more active compound into the brain versus amisulpride than the daily dosing of patients can potentially be decreased. All published materials on amisulpride AEs suggests that side effects are dose dependent
- We expect that LB-102/103 will improve the risk/benefit profile as compared to amisulpride. It is important to note that if approved, LB-102/103 would be the first benzamide marketed in the U.S. for the treatment of schizophrenia

PATENTABILITY OF LB-102 AND LB-103

- US Federal Court (Proctor & Gamble v Teva, 566 F.3d 989, 996) affirms that a presumption of obviousness is overcome when there is no reasonable expectation of similar properties

- *A priori* there is no way to know if addition of a single methyl group to amisulpride would increase or decrease binding to dopamine or other active receptors

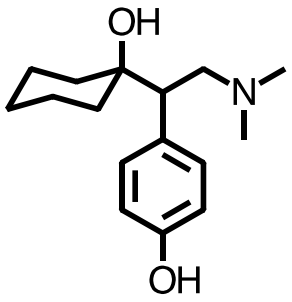
  - Balance of electronic (additional H bond accepting ability) versus steric (extra bulk of CH_3) governs ligand/receptor interaction

  - This was unknowable prior to LB completing its experiments

- Many examples of structurally similar molecules have been patented and enjoyed years of market exclusivity

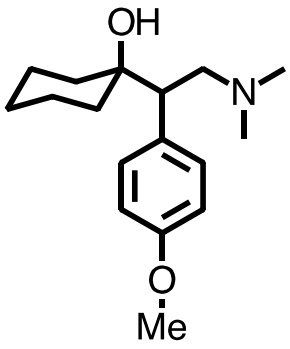
- LB patent attorney at Perkins Coie assisted in the preparation of both provisional patent applications (original and amended), and are of the opinion that these patent claims will be enforceable

PATENTED METHYLATED ANTIPSYCHOTIC



Desvenlafaxine (PFE, Pristiq), US Patent 4,535,186, COM as HCl salt, filed 10/26/83 by AHP. Succinate, US Patent 6,673,838, filed 2/11/02 by WYE

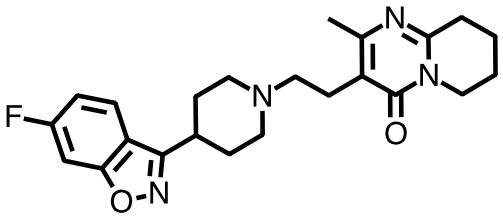
Paragraph IV (P IV) challenge filed in 2012 (litigation was not related to COM claims), generic launched in March 2017



Venlafaxine (PFE, Effexor), US Patent 4,609,758 COM, filed 05/09/85 by AHP. XR patent, US Patent 6,274,171, filed 1/20/00 by AHP on XR form based on MCC

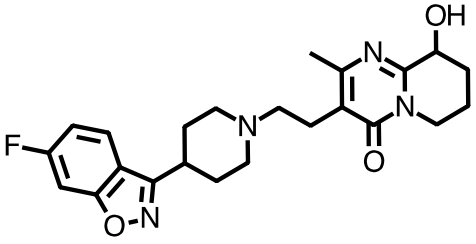
P IV challenge from IPXL (also not related to COM claims) in 2006 settled 2008, generic launched in June 2010

PATENTED HYDROXYLATED ANTIPSYCHOTIC



Risperidone (JNJ, Risperdal), US Patent 4,804,663 COM, filed 2/5/86 by Janssen

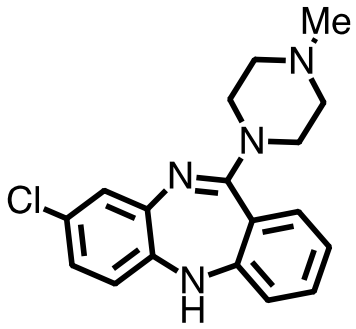
Apotex filed P IV in 2006 and lost on appeal in 2008



Paliperidone (JNJ, Invega), US Patent 5,168,952 COM, with a priority date of 11/7/88 by Janssen. Subsequent claims and pediatric exclusivity extended patent life through 10/9/12

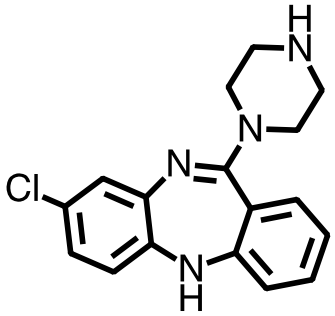
Generics launched 2015 (AGN, MYL)

PATENTED DESMETHYLATED ANTIPSYCHOTIC



Clozapine (HLS, Clozaril), US Patent 3,539,573 COM, filed 10/21/68 by Jean Schmutz

Generics launched in December 1997

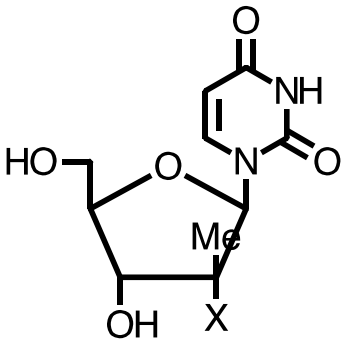


ACP-104 (ACAD, Desmethylclozapine), US Patent 7,491,715 COM, filed 5/3/06 by ACAD (cip of 10/761,787, filed 1/21/04)

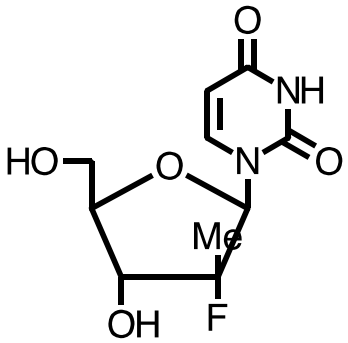
Failed clinically but patent not invalidated

GILD/MRK (VRUS/IDIX) EXAMPLE

IDIX (US Patent 7,608,597, filed 6/20/03) claimed all methyl halogen versions of the C-2' modified uridine to treat HCV, but only reduced to practice claims for the Cl, Br, and I versions



Where X = Cl, Br, I.

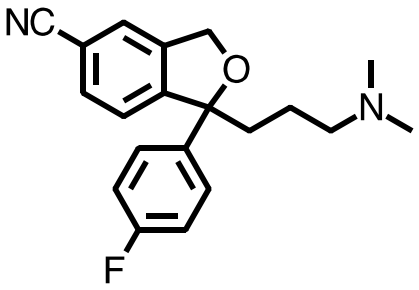


Sofosbuvir

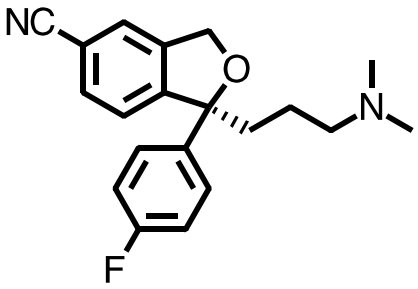
VRUS (US Patent 7,429,572, filed 4/21/04) claimed *and enabled* the fluorine halogen version of C-2' modified uridine to treat HCV which later became Sofosbuvir

GILD bought VRUS and MRK bought IDIX. MRK sued GILD for infringement and was initially granted $2.5 billion in royalties (12/16), which was overturned on appeal by GILD (6/17)

ENANTIOMERS ARE PATENTABLE



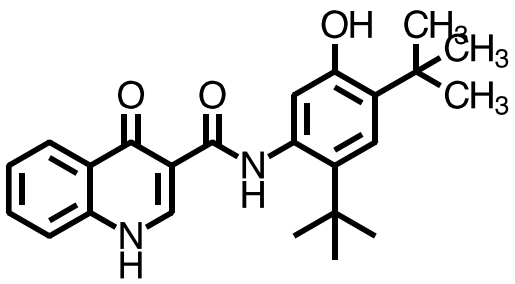
Citalopram (FRX, Celexa), US Patent 4,136,193 COM, filed 1/7/77 by Kefalas



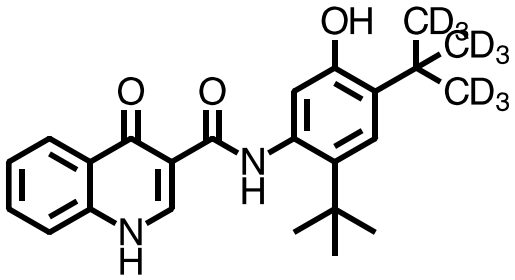
Escitalopram (FRX, lexapro), US Patent 4,943,590 COM, filed 6/8/89 by Lundbeck

FRX' patent was upheld in a 2006 case against Teva. Generic approved in March 2012

DEUTERATED ANALOGS ARE PATENTABLE



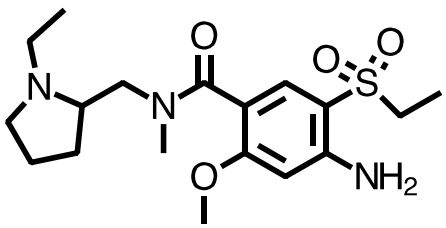
Ivacaftor (VRTX, Kalydeco), US Patent 7,495,103 COM, filed 6/24/04 by VRTX



CTP-656 (CNCE), US Patent Application 053323 COM, filed 9/23/16 by CNCE

VRTX acquired rights in March 2017 for $160 million upfront and up to $90 million in milestones. CNCE had begun a P2 study in December 2016

ALKERMES *N*-METHYL AMISULPRIDE



- ALKS has filed 2 patent applications (14/702,967, filed 12/23/10, & 13/335,405, filed 12/22/11) to allow multiple loading of a polymer for sustained release
- No efficacy data have been reported publicly
- The USPTO issued a final rejection to the first application on 2/10/17. ALKS filed an appeal on 7/20/17. The second application was abandoned on 11/5/15
- Claims 22 and 23 of initial application includes amisulpride (together with apriprazole, asenapine, cparprazine, citalopram, dehydroaripriprazole, escitalopram, galantamine, iloperidone, latrepirdine, lurasidone, olanzapine, paliperidone, perospirone, risperidone, or ziprasidone
  - Subsequent claims mention dozens of other CNS drugs
  - These claims were cancelled in a revised version filed 10/13/15, which does not include any claims to amisulpride
- The application does not provide any data reducing claims on amisulpride to practice and, to the best of our knowledge, have never been disclosed

ACACIA PHARMACEUTICALS

- Acacia is developing an injectable form of amisulpride (Baremsis/ADP421) for treatment of post operative nausea & vomiting
- A 2/13/17 PR claimed that the company aimed to submit an NDA in the first half of 2017
  - As of 7/24/17 no PR of such a filing has been released
- Acacia has a US patent (9,545,426, filed 3/11/10) covering dosing of up to 20 mg amisulpride by IV injection, orally, rectally, intramuscularly, subcutaneously, topically, intranasally, or transdermally
  - Patent does cover use of S enantiomer (at doses up to 20 mg)
- An earlier patent (8,686,019, filed 3/11/10) covers doses up to 40 mg
- By comparison, the typical dose of amisulpride to treat schizophrenia is 800 mg/day

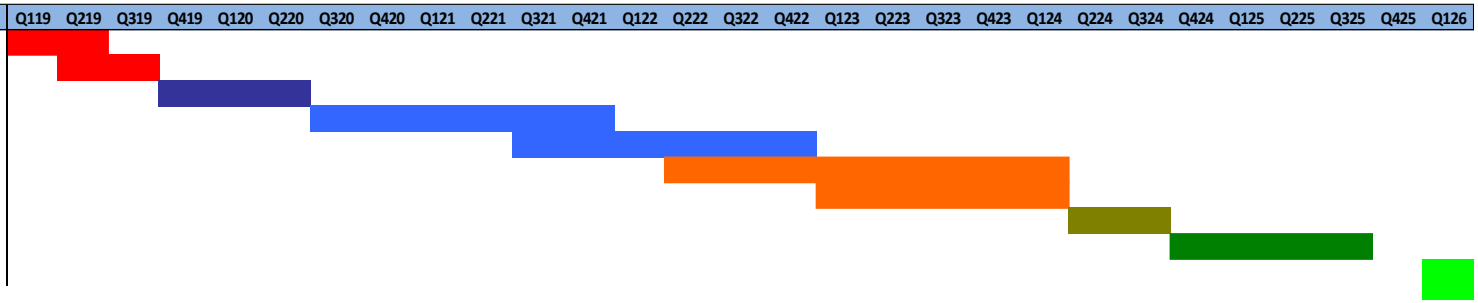
PROJECTED IND ENABLING STUDY TIMELINE

IND Opener enables Phase 2A POC. DDI studies help with inclusion/exclusion criteria and allow to determine if LB-102 is comparable to amisulpride in DDI potential.

IND could be filed on month 12 after study initiation (does not take into account contractual time spent choosing vendors)

PROJECTED TIMELINE TO APPROVAL

Study No.	Description	Duration
LB-102-101	Phase 1, n = 40, SAD	2 weeks
LB-102-102	Phase 1, n = 40 MAD	2 weeks
LB-102-201	Phase 2a, n = 40	4 weeks
LB-102-202	Phase 2b, n = 300*	6 weeks
LB-102-203	Phase 2b OLE n = 100	1 year
LB-102-301/302	Phase 3, 2 X (n = 600)	6 weeks
LB-102-303	Phase 3 OLE (n = 300)	6 months
	NDA prep	
	NDA	
	MKT	



* Statistically powered to see ~10 pt difference between PBO and 102, assuming 45% dropout rate, SD = 20, alpha = 0.9

ICH guideline: 100 patients exposed for more than one year, 300-600 patients exposed for at least 6 months and 1500 patients exposed total.