Companies: Adolor (ADLR) and Progenics (PGNX)
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We have reviewed 11 year-old Adolor Corporation previously and, in so doing, also noted Progenics Pharmaceuticals Inc. which was at least a year behind Adolor with a directly competitive drug. Both companies target ileus (constipation) caused by 1) post abdominal surgery (post-operative ileus, POI) or 2) chronic use of opioid analgesics like morphine (opiate bowel dysfunction, OBD).

We have been very skeptical of Adolor's ("Entereg" or "alvimopan") results from three clinical trials for the POI indication. Last June 28, the Company submitted its NDA which was accepted under a Standard Review of 10 months. On April 19, the PDUFA date was extended for 90 days, allowing FDA to review the results from a fourth clinical trial run by Adolor's partner, GlaxoSmithKline. This trial failed to demonstrate statistically significant efficacy versus placebo. Adolor's PDUFA date is now July 25. Given the mixed data at best, an "approvable" action by the agency seems most likely.

Progenics's 19-year history is less focused than Adolor's. Begun in late 1986, the Company was developing cancer vaccines (melanoma, colorectal, gastric and small cell lung cancers), migrated into treating HIV infection and, in October 2001, licensed methylnaltrexone ("MNTX") to treat ileus.

Progenics's and Adolor's valuation metrics at June 7 close were a market capitalization of $385 million (stock at $19.64, 19.6 million O/S, $60.6 million COH at March 31) and $359 million (stock at $9.18, 39.1 million O/S, $162 million COH), respectively. For Progenics, the cash and new shares from a secondary offering in early April are included.

Conclusion: Adolor is likely to receive an "approvable" letter from FDA on or before Monday, July 25 which should cause the stock to drop. Progenics should benefit from Adolor's delay to market and should rise.

Clinical Status

Adolor

Entereg (aka alvimopan, '2698) is a derivative of loperamide (trade name Imodium) originally developed by Lilly and tested as a laxative (the opposite of Imodium's activity). In June 1998, Adolor licensed '2698 from Robert's Shire unit for $300,000 up-front plus $1.9 million in milestones. Upon FDA approval, Adolor will pay Lilly a $500,000 milestone. Dosed as a pill, '2698 remains in the GI tract where it can block the inhibition of peristalsis by morphine-based narcotics. Since '2698 is not absorbed, narcotics retain their full CNS activity (pain ablation). Although Adolor's *in vitro* and Ph 1 experiments ('2698 caused no loss of analgesia in patients getting molar extractions while using morphine) support this hypothesis, the potential for clinical utility in POI is less clear, since there are no exogenous opioids used during surgery e.g., in bowel resections or hysterectomies.

Adolor completed three Ph 3 clinical trials and submitted an NDA to FDA on June 28, 2004. Accepted for filing in early September, a fourth trial conducted by Adolor's partner, GlaxoSmithkline was added to the NDA package, leading to a 90-day extension of the PDUFA date from April 25, 2005 (ten months) to July 25. All four trials are summarized (raw database format) below.

Included is a fourth, safety only study (#306), included for completeness (Entereg appears safe).

4/2/03: Q1/03E: Ph 3 data (*#302; 1st*) of *'2698* in POI; Of 451 enrolled, 449 *ITT*, 427 as *mITT*; PCE SS for 1) PCE, 6mg ($p<0.01$), not 12mg ($p=0.11$)! (see 6/28/01 for opposite result) and 2) SCE (hospital discharge order), 6mg ($p<0.01$), not 12mg ($p=0.19$)!; maximum dosing was 7 days (not 21 in original design); Dropout was placebo (N=32/*153*, 21%), 6mg (N=24/*150*; 16%), 12mg (N=39/*146*; 27%); Modified ITT omits 22 Pt.s who did not receive opioids or who received different surgery than planned;

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9/23/03: Ph 3 data (*#313; 2nd*) of *'2698* in POI; Of 510 enrolled, 469 as *mITT* PCE SS for 1) PCE, 6mg (N=155, 129 completed; *p<0.05*, hazard ratio 1.28; mean 105 hours), 12mg (N=165, 141 completed; *p<0.01*, hazard ratio 1.54; mean 98 hours) vs placebo (N=149, 115 completed; mean 120 hours) and 2) SCE (hospital discharge order), 6mg (*p=0.07*; mean 13 hours sooner, hazard ratio 1.25), 12mg (*p=0.003*; mean 20 hours sooner, hazard ratio 1.42) vs placebo (time not given, average "4.2 days," only if actual discharge is on calendar day of written order); Dropout was placebo (N=34/*149*, 23%), 6mg (N=26/*155*; 17%), 12mg (N=24/*165*; 15%);

1/13/04: Q1/04E: Ph 3 busts (*#308; 3rd*) for *'2698* in POI; Of 666 Pt.s, 6mg (p=.079), 12mg (p=.038), but Bonferroni required p≤0.025; PCE upper&lower GI recovery;

12/23/04: **GLAXO:** Ph 3 busts (#101) *in Europe, ANZ* for *'2678* in POI; PCE upper&lower GI recovery; 6mg (p=0.042), 12mg (p=0.20) vs placebo; Bonferroni required p≤ 0.025; Time to hospital discharge order not SS; SCE of GI function (solid food tolerance, crapping) were SS; DB-PC of N=741 (bowel resection); Another 170 radical hysterectomy also treated, not in PCE, no data;

10/03: **SAFETY;** Ph 3 "data" (*#306; 4th* safety only) in 519 Pt.s; placebo (N=100) or 12mg b.i.d. (N=400), PRN up to 7 days;

A synopsis of the above data is shown below in tabular form noting the p-value for the primary clinical endpoint at each dosage in each of the four clinical trials. Statistically significant results are underlined.

	6mg	12mg	Notes
#302	p≤0.01	p=0.11	The absence of efficacy at 12mg is puzzling in light of the results with 6mg.
#313	p≤0.05 (marginal)	p≤0.01	These are the best results obtained.
#308	p=.079	p=.038	Bonferroni required p<0.025 in either arm.
#101	p=0.042	p=0.20	Bonferroni required p<0.025, as above.;

Thus, of four trials, only one demonstrated a statistically significant result at the intended dosage of 12mg. Given the lack of medical necessity and the relative simplicity of getting patients to "walk-the-halls" to reinitiate peristalsis after abdominal surgery, the FDA is likely to designate Adolor's Entereg as "approvable," but contingent on at least one more clinical trial demonstrating a statistically significant improvement in upper and lower GI function.

Progenics

In October 2001, Progenics acquired WW rights to methylnaltrexone for opioid bowel dysfunction (*OBD*), from UR Labs (Reno, Nevada), which was assigned the October 1999 patent rights to the molecule by the University of Chicago (Drs. Yuan and Moss). At least 12 clinical trials had been completed in a total of 348 patients, all under physician INDs.

The Company is testing three delivery routes for three different indications, complicating the story. Unlike Entereg which does not escape the GI tract, MNTX simply does not cross the blood brain barrier. Thus either drug can reduce the peripheral side effects from opioid use without interfering with pain reduction. The drug delivery routes contemplated by Progenics are sub-cutaneous injection (for *OBD* in AMI, advanced medical illness, i.e., patients in hospice care), intravenous (for *POI*), and oral (for OBD of chronic pain). A summary of the relevant trials (raw database format) is below.

AMI - Sub-Q dosing - This is Progenics's most advanced indication for MNTX.

2/22/02: Progenics-sponsored Ph 2 begins for sub-Q *methylnaltrexone* in AMI, open-label;

12/20/02: Ph 2 "data" for sub-Q *methylnaltrexone* in AMI, open-label, single arm; Of 33 to be enrolled, 29 Pt.s (*5.0-*, *7.5-*, *10-*, *12.5mg*) sub-Q, every other day, 3 dosings, for 1wCOT (TIW), then, 3w OLE (PRN dosing); All data only from extension phase; PCE of % laxating at 4hFU was *26-*, *48-*, *57-*, *67%*);
No placebo, no N= and *blinded* dose range was 1.0-20mg); No data from 1wCOT;
and Ph 3 begins (*1st*) for sub-Q *methylnaltrexone* in AMI; DB-PC (3 cohorts) in 150 Pt.s at 25 US sites w/ single, sub-Q dose at 0.15- or 0.30mg/Kg (= 12-24mg/80kG); Pt.s are cancer, CV, AIDS on opioids; 20 sites are hospice; PCE is laxation w/in 4 hours; 4wOLE, too; Data by YE'03E, NDA filing in '04E; Neither done;

4/30/03: Ph 2 data for sub-Q *methylnaltrexone* in AMI; DB (no placebo); 33 pt.s (4 dosages) at 1.0-, 5.0-, 12.5- or 20mg dosage on days 1, 3, 5 for 1wCOT; Hit PCE of laxation w/in 4h of dosing; Combined 3 upper dosages (*60%*) vs 1.0mg (*8%*), $p \leq 0.0001$; Also 3w OLE followed;
Weight-based dosing (retrospective analysis) in Ph 3 probably OK;

6/2/03: ASCO (#2933); Ph 2 data for *methylnaltrexone* in AMI, as above; Time to laxation > 48h at 1.0mg; 58% (combined active dosages) laxated w/in 4 hours; No SAE, cramps (43%), flatulence (21%), no ↑ pain meds; 3wCOT OLE started at 5mg, escalated to laxation; In blinded phase, 1.0mg (N=10), 5.0mg (N=7), 12.5mg (N=10), 20mg (N=6); Median weight 61Kg (135 lbs; 15_, 18_); Expected survival was 1-6 months, 28 cancer, 3 sickle cell, 2 AIDS;
PR: 58% success (3 higher dosages) after 4wCOT (blinded+OLE); No dose-response, and *42% failed*;

1/13/04: Ph 3 begins (*2nd*) for sub-Q *methylnaltrexone* in AMI; DB-PC in 130 Pt.s at 16 N.Am. hospice sites w/ sub-Q dose every other day (0.15- or 0.30mg/Kg) for 2wCOT; PCE is laxation w/in 4 hours; *12w OLE*, too; Higher dosage only after no laxation at 1wFU;

12/3/04: Q1/04E: Ph 3 enrolled (*1st*) for sub-Q *methylnaltrexone* in AMI; DB-PC in 150 Pt.s; *4w OLE*, down from *12w OLE*;

3/10/05: 12/03E: Ph 3 data (*1st*) for sub-Q *methylnaltrexone* in AMI; DB-PC (0.15- or 0.30mg/Kg) in 154 hospice Pt.s (most at home) at 16 sites; PCE is % who 1) poop in *4 hours* after 1 dose; MNTX (0.15mg/Kg; *62%*) vs (0.30mg/Kg; *58%*) vs placebo (*13%*), $p<0.0001$ for both dosages → No dose response; 2) SCE: poop in *24 hours* (68%, 64%, 33%; $p \leq 0.001$ both arms) → No dose response; 3) SCE: median time to poop (70 minutes, 45 minutes, >24 hours; $p \leq 0.0001$ both arms);

mid-05E: Ph 3 enrolled (*2nd*) for sub-Q *methylnaltrexone* in AMI;

12/05E: 2004E: NDA submission for sub-Q *methylnaltrexone* in AMI (opioid);

POI - IV dosing - This is Progenics's second most advanced indication for MNTX, not yet in Phase 3 testing.

6/02: ASCO (#1501); Ph 1 data from 12 people; Dosed IV *methylnaltrexone* at 0.45mg/Kg (or, 5/13/03, 0.30mg/kg)?; Also, Ph 2 data as DB-PC in 22 Pt.s dosed IV at 0.1mg/Kg; 0% laxation in placebo vs 100% w/ drug;

5/13/03: Ph 2 begins for IV *methylnaltrexone* in POI; DB-PC in 60 colectomies; PCE restore bowel function, ↓ duration, severity of POI; Typical ileus post-colectomy is 5 days(true?); Post-surgical dosing, placebo vs 0.30mg/Kg q.i.d., until restored function, discharge eligibility;
Also Ph 1 data show ↑ motility in 12 people dosed IV, q.i.d. for 3dCOT;

10/7/04: Ph 2 enrolled for IV *methylnaltrexone* in POI;

H2/04E: Ph 2 begins for IV *methylnaltrexone* in POI; DB-PC in hysterectomy; Not done, none planned at 6/05 (see below);

1/20/05: Q2/04E: Ph 2 weak for IV *methylnaltrexone* in POI post-colectomy; DB-PC as post-surgical MNTX (0.3mg/Kg) q.i.d. for ≤ 7dCOT vs placebo in 65 Pt.s at 8 sites; Mean values for 1st solid meal (p=0.12), 1st poop (accelerated 23 hours, p=0.01), 1st poop/solid meal (*p=0.06*), time to discharge eligibility (30 hours; p=0.03); TTD (25 hours; p=0.09);

6/7/05: E-mail from Co.; "No imminent plans for hysterectomy trial;"

OBD - Oral dosing - This is Progenics's least advanced indication for MNTX.

11/21/03: Ph 1 begins for oral *methylnaltrexone* in OBD (*chronic* pain); DB-PC in 35 people, 3 dosages;
5/25/04: Ph 1 data for oral *methylnaltrexone* in OBD; 2 formulations at 3 dosages in 61 people;
Q2/05E: H2/04E: Ph 2 begins for oral *methylnaltrexone* in OBD;

Progenics's most advanced program, in AMI, addresses a fairly small US market of roughly one million patients under hospice care. In addition, by definition, most of these patients will require the drug for less than 60 days; in fact, the median LOS under hospice care is 25 days. The Company's second indication, in POI, is still in middle stage testing with modest results, at best, reported from a Phase 2 trial. Although Progenics had planned to expand POI testing to hysterectomy patients (like Adolor) during 2004, there are no imminent plans to expand beyond the colectomy indication. At ten percent of the 40 million surgeries each year, POI is a larger potential market than AMI; however, Progenics is perhaps a year behind Adolor for this use. Also, like AMI, a POI indication contemplates limited utilization (5-7 days) which, without a demonstrated decreased hospital LOS, may face reimbursement hurdles. Finally, OBD is the home run indication for both companies since it encompasses roughly four million chronic users in the US on daily opioids. For Adolor, GlaxoSmithKline controls Alvimopan's destiny in this indication. For Progenics, the Phase 2 trial is expected to begin this month.

If Progenics is able to submit its first NDA for MNTX by year end, as planned, it is conceivable that off-label usage (sub-Q rather than IV dosing, in OBD) could take hold, since both routes of administration target the same underlying pharmacology, opioid-dependent bowel dysfunction.

Risk Assessment

- *Inconsistent Phase 3 Data* Adolor's action letter from FDA, due July 25 is likely to get an approvable notice, requiring a second Ph 3 trial to demonstrate efficacy in POI. The PDUFA 90-day extension, nominally to incorporate GlaxoSmithKline's Ph 3 data, only confirmed the sub par results Adolor's trials have demonstrated previously. A short position in Adolor is warranted.

- *Early stage clinical development* Progenics, with a tarnished history in drug development and at an earlier stage of clinical development for MNTX, will benefit from Adolor's delayed market entry. In addition, the Company's first Ph 3 trial in AMI was clearly positive. The second Ph 3 trial should complete enrollment soon with top line data available three months later. Since the single dosing used in the first Ph 3 was successful, multiple, every-other-day dosing is likely to succeed as well. A long position in Progenics is warranted.