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Company: Regeneron Pharmaceuticals, Inc. (REGN)
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We recently identified Regeneron (REGN) for review (short thesis) using our rough screen for companies with 1) relatively high market capitalizations based on 2) excessive optimism in anticipation of clinical trial results from the company's first product. The analysis below is preparatory, as additional questions need answering by Regeneron (which has not returned my calls or E-mail) and possibly several outside sources.

After the close on October 31, Regeneron reported Q3 results (FYE December), noting $341 million of cash and liquid securities, which includes $200 million of long term debt (see below). The stock closed at $15.13, giving Regeneron a market capitalization of $665 million based on 44.0 million shares outstanding (20.7 million float). The significant short position for the prior three months (July to September) had been flat at ≈ 8 million shares (25-30 days) and dropped to 7.4 million shares (18 days) in October. As noted above, last October Regeneron issued a $200 million, 5.5 percent, 7-year note convertible at $30.25. The company is expected to burn ≈ $120 million in FY'02 and moderately more in FY'03.

Conclusion: *Regeneron will be a strong "short" candidate. The company's clinical trials with Axokine for obesity are at very high risk of clinical, regulatory and, if approved, market failure. Patient enrollment has been completed for ≈2,600 patients in three Phase 3 trials. Adverse events causing abrupt termination are possible but unlikely at this stage. Therefore, results can be expected to be reported, as Regeneron has indicated, in "Spring 2003." Stock price appreciation this quarter (to at least the low 20's) and timing (in Q1/03) should guide the investment decision.*

Introduction: Almost fifteen years old, Tarrytown, New York-based Regeneron Pharmaceuticals has raised almost $600 million. Regeneron currently has no products. The company was founded on the potential utility of ciliary- or brain-derived neurotrophic factors (*CNTF and BDNF*, respectively) to treat neurodegenerative diseases like amyotrophic lateral sclerosis (ALS, aka Lou Gherig's disease).

Amyotrophic Lateral Sclerosis

ALS was first described in 1869 by the French neurologist, Jean-Martin Charcot. It is a fatal, neuromuscular (progressive degeneration of motor neurons) disease affecting ≈ 30,000 U.S. citizens. Median survival after diagnosis is 3.5 years with death often due to respiratory failure. Only Aventis's (RPR) Rilutek (riluzole) has been FDA approved (12/95) and that was based on improved survival data. In 1994, Regeneron reported that its Ph 2/3 trial of CNTF (later named *Axokine*) had failed in ALS. In early 1997, Regeneron (then partnered with Amgen) reported that its advanced clinical trial of BDNF had also failed in ALS.

In the original CNTF trial for ALS, ≈ 480 patients were treated with either 15- or 30µg/kG by subcutaneous self-injection three times per week for nine months. Side-effects, including anorexia, weight loss and cough, were dose-limiting in many patients. Nevertheless, Regeneron has pursued the use of CNTF to treat obesity since the Fall of 1997.

Obesity

A national problem, there are only two prescription drugs approved for obesity, Abbott's Meridia (sibutramine; tested in > 6,000 patients; '01 sales of $202 million) and Roche's Xenical (orlistat; tested in > 7,000 patients; '01 sales of $636 million). Neither drug is routinely reimbursed by third party payors. Also, 18 months after an April 1996 approval, FDA withdrew Interneuron's Redux (D-fenfluramine, aka *"fen"*) from the market due to heart valve damage putatively linked to its (off-label) combined use with Wyeth's Phentermine (aka *"phen"*). Meridia and both "fens" raise brain serotonin levels while Xenical prevents triglyceride catabolism, preventing fat absorption by the intestines. The mechanism of action for

CNTF is different from the other drugs but is also speculative at this time. Finally, in November 2000, the 50 year-old, GRAS-listed OTC appetite suppressant phenylpropanolamine (e.g. Dexatrim, Acutrim) was withdrawn from the market due to a 15-fold increased risk of hemorrhagic stroke in women.

Because of the potential for off-label use by a very large population, the low risk of non-medical (life style) solutions, the fen-phen fiasco and the still contentious issue of whether moderate obesity is a "disease," FDA tends to be especially conservative towards novel obesity drugs. Still, given the general failure of on-again/off-again weight-loss programs (the "rhythm method of girth control"), many people are in genuine need of medical intervention.

Regeneron is also in the clinic with various soluble receptors (aka *TRAPs*) for oncology, rheumatoid arthritis and asthma. However, Regeneron's valuation over the next 3-6 months will rest solely on the clinical progress of Axokine to treat obesity, the focus of this report.

Axokine for Obesity

Below is a summary of Axokine's (CNTF) clinical history. These are my raw notes from the database.

1/30/92:	*ODS* for CNTF in *ALS*.
1994:	Ph 2/3 busts for *CNTF* in ALS; DB-PC of 730 pt.s (15-, 30µg/Kg), self-injected Sub-Q 3x/week for 9 months; PCE was rate of ↓ muscle strength; SCE were FEV, survival; Side-effects included anorexia, weight loss, cough; See Neurology, 46, 1244-1249, 1996; "dose-limiting in many patients."
5/96:	Neurology (46), 1244-49; Ph 2/3 data of *CNTF* in ALS; Weight loss was 30 µg/Kg (*6.3%*±0.7 or *9.7lbs*±1.1), 15 µg/Kg (*7.4%*±0.6 or 11.8*lbs*±0.95), placebo (4.5%±0.5 or 6.9*lbs*±0.8); 134 ALS Pt.s were 9 months on drug w/ no neutralizing Ab → Of 241 enrolled (30µg/Kg), 63 dropped out = 178, and 82% (128) had Abs, 70% (125) neutralizing, so 30% (53); Of 244 enrolled (15µg/Kg), 24 dropped out = 220; and 75% (165) had antibodies, 63% (139) had neutralizing, so 37% (81);
5/14/97:	NYT; $75M, 10-year (5-year R&D) w/ **P&G** + $43M equity (4.4M at $9.87; 13.7% post) + $17M over next 5 years as stock (up to 20%); Stock up 51% to $12'ish; R&D rights for "small drugs" for bone, CV, muscle, cancer (angiogenesis);
9/97:	**P&G** amends to $15M, deal, adds Axokine, now targeting *obesity* in Type 2 diabetics;
11/14/97:	**Q3; $127M COH**; 1st SEC document to mention obesity;
9/2/99:	**P&G** bails on *Axokine* for obesity; drug exacerbated (HSV) cold sores; remaining R&D support for at least 3 years; Co. continues for Pt.s w/o HSV infection;
Q4/99:	Ph 1 done for *Axokine* for obesity w/ 2wFU;
3/9/00:	Paying up to $31M to Emisphere for (oral formulation of) *Axokine* in obesity;
3/28/00:	Ph 2 begins for *Axokine* in obesity; DB-PC dose-ranging (≤ 2µg/Kg) sub-Q in 175 Pt.s for 90 days; Dosage lower than used w/ HSV reactivation problem. Prior HSV infection is not exclusionary for the Ph 2.
7/10/00:	Ph 2 enrollment done for *Axokine* in obesity; 3 month treatment;
11/28/00:	WSJ PR; Ph 2 data for *Axokine* in obesity; 12wFU of 170 (5 cohorts of 34 each) obese (BMI 35-50; average weight 250 lbs) Pt.s (80% _) at 7 US sites, self-injected, q.d. sub-Q; DB-PC, dose-ranging: PCE-*1 (N=87*), weight change from baseline at 12wFU in "completers" placebo (N=19, 40% dropout; ±1.3), (0.3µg/Kg (N=23, 25% dropout; -3.4 lbs), 1.0 (N=26, 30% dropout; -8.9), 2.0 (N=19, 42% dropout; -7.5); 5th (not part of primary analysis) was 8 weeks at 1.0, then (blinded) placebo for 4 weeks); PCE-*2 (N=132*), weight change in ITT (last observation carried forward); (0.3µg/Kg (N=31; -2.4 lbs), 1.0 (N=37; -7.5), 2.0 (N=33; -5.8), placebo (N=31; ±0.6); 1.0 µg/Kg will be used in Ph 3; 5th group did not (rebound) regain during 4w placebo or at 24wFU. No dose response at 2.0?
2/28/01:	PR Keystone Meeting; Ph 2 update (1st) for *Axokine* in obesity; Weight loss maintained 1) at 12wFU after 12 week treatment and 2) at 16wFU after 8 week treatment; Of 4 cohorts, 12 week "completers" totalled (N=67 of theoretical 136); For 12 weeks on drug, then 6-, 12 weeks post: placebo (N=15; ±1.7, ±2.9, ±3.8 lbs); 0.3µg/Kg (N=16, -4.6, -4.9, -4.2), 1.0 (N=19; -9.7, -11.0, -10.8), 2.0 (N=17; -7.6, -7.6, -5.5); No dose response?

7/31/01: PR: Ph 3 begins (#1) for Axokine in obesity; 12m treatment of 2k Pt.s (3:1) at 60 US sites, DB-PC, q.d. sub-Q injection at 1µg/Kg; BMI range is 30-55 (w/o obesity risk factors) or 27-55 w/ hypertension or ↑ lipids (but no diabetics); After 12m treatment, all Pt.s on drug, open label for 12 months for safety; PCE is weight change from baseline during treatment period; Additional Ph 3 studies (e.g., diabetics) will enroll another 2k Pt.s.
and PR: Ph 2 update (2nd) for *Axokine* in obesity; *33% dropout rate:* Of 136 theoretically enrolled, only 91 completed 12 weeks treatment; For 4 cohorts, 12 week "completers", then 6-, 12-, 24-weeks post: placebo (N=23/+0.2, N=19/+2.2, N=19/+1.9, N=15/+4.0 lbs); 0.3µg/Kg (N=23/-3.5, N=22/-4.7, N=18/-4.8, N=18/-4.4), 1.0 (N=26/-9.1, N=25/-9.6, N=23/-9.9, N=19/-12.4), 2.0 (N=19/-8.0, N=18/-7.8, N=17/-5.8, N=12/-5.4); Dose response? 2.0 group consistently did worse than 1.0, which did better than 0.3; PCE is 5% greater weight loss than placebo at 1yFU or portion of population on drug losing >5% greater than portion on placebo losing 5%.

9/11/01: PR; Ph 2 update (3rd) for *Axokine* in obesity; Of 4 cohorts, 12 week "completers" totalled (N=91 of theoretical 136); For 12 weeks on drug, then 6-, 12-, 24- and 36-weeks post: placebo (N=23/+0.2, N=19/+2.2, N=19/+1.9, N=16/+3.8, N=16/+3.1 lbs); 0.3µg/Kg (N=23/-3.5, N=22/-4.7, N=18/-4.8, N=18/-4.4, N=17/-2.9), 1.0 (N=26/-9.1, N=25/-9.6, N=23/-9.9, N=19/-12.4, N=17/-12.4), 2.0 (N=19/-8.0, N=18/-7.8, N=17/-5.8, N=12/-5.4, N=11/-3.9); No dose response?

11/16/01: Ph 3 enrollment done for *Axokine* in obesity; However, Pt. may not have begun treatment until 1/03;

1/9/02: PR at H&Q; 2k Pt.s at 65 US sites; 4% dropout rate, but only average of 8w in study; 12mFU end 1/'03

2/02: Co. reports 1 case of (very rare) Guillain-Barre in *Axokine* arm of Ph 3; Also, Bell's Palsy and HSV reactivation seen in earlier studies; All suggest a CNTF-dependent peripheral neuropathy side-effect;

4/9/02: PR; Ph 3 begin (#2 and 3) for *Axokine* in obesity; 300 Pt.s each (BMI 27-50) at 20 US sites, DB-PC; 1) *Treat for 6mCOT*, then 6mFU and 2) *treat for 3mCOT*, then 9mFU; After 12 months, re-treat (drug or placebo) w/ 6mFU (18 months total); PCE is weight loss at 12mFU (vs weight loss after 12m treatment);

6/2/02: NYT; CEO Schlieffer sounds rather optimistic; COB Vagelos: "This company cannot ultimately fail."

6/13/02: PR; Ph 3 begin (#4) for *Axokine* in obesity; DB-PC in 180 (0.5-, 1.0 µg/Kg/day) *diabetic Pt.s* (BMI 27-45) at 12 US sites for 12 weeks, then re-randomize all 180 pt.s into 2 dosage groups for 12 weeks;

7/25/02: PR; Ph 3 enrollment done (#2 and 3) for *Axokine* in obesity;

Q1/03E: Ph 3 data for *Axokine* in Spring; Last Pt. 12mFU ends 1/03;

A careful review of the Phase 2 data and several Phase 3 trial designs reveal the inherently experimental clinical development program Regeneron has chosen for Axokine. Specifically:

1) The Phase 2 trial employed a *12-week* treatment period and the PCE of this dose-ranging study was (presumably) weight change from baseline *during the treatment period*. Subsequent updates were provided for treated patients at 6-, 12-, 24- and 36-weeks post-treatment. Note below that the designs of all four Phase 3 trials differ significantly from this, Regeneron's only Phase 2 study.

2) The first Phase 3 employed a *12-month* treatment period and the PCE was, as above, weight change from baseline *during the treatment period*. The rational for this dramatic shift in treatment period is unknown.

3) The second and third Phase 3 trials employ *6-month* and *12-week* treatment periods respectively; but, both have PCEs of weight loss at 6-months and 9-months *after the treatment period*.

4) The fourth Phase 3 combines a dose-ranging study (two dosages), an as yet *untested patient population* of diabetics and two, 12-week treatment periods. The trial is small (60 patients per cohort) and involves a re-randomized cross-over study. This is a Phase 3 trial in name only. The results can not support a label-expanding registration and run the genuine risk, like any experiment, of disappointing investors anxious to see Regeneron enter the diabetes market.

5) There was no *dose-response* effect observed in the Phase 2 trial and, more importantly, the 2.0 µg/Kg dosage was consistently inferior to the 1.0 µg/Kg dosage. Since the drug was originally tested and weight loss was observed at 15- and 30 µg/Kg, it makes no sense that 1.0 µg/Kg is "optimal" and 2.0 µg/Kg is significantly worse. Put differently, Axokine's efficacy should not have fallen so dramatically between 1.0- and 2.0 µg/Kg given that efficacy was originally observed at 15 µg/Kg. This observation alone suggests a serious flaw in the Axokine story.

6) Data from the Phase 2 trial suggest a *dropout* rate of at least ≈ 35 percent. Assuming randomized enrollment of 170 patients across five arms (34 patients on placebo and each of three dosages plus an early termination cohort). This resulted in very small net populations of 15-25 in each cohort. Regeneron has not provided true ITT results for the expected 136 patients enrolled in the four cohorts indicated for primary analysis. It is not clear how a "last observation carried forward" analysis resulted in data for only 91 patients (*see the 9/11/01 DB entry on page 3*).

There are several other problematic aspects of Axokine's clinical development history. These include:

7) If the dropout rate in the Phase 3 trials is as large as observed previously, *additional clinical testing* may be required. Regeneron plans to test over 4,000 patients with Axokine; however, the variability in multi-trial design may interfere with having a single, sufficiently large data set on which to base a drug dosage regimen or FDA approval.

8) Regeneron has postulated that CNTF acts by binding to receptors in the hypothalamus to "suppress appetite and reduce body weight." Since there is no indication that Regeneron's clinical trials included behavior modification/life style coaching (diet/exercise), it is difficult to understand how the weight loss observed after 12 weeks of treatment was *sustained* after nine months off drug. If the drug was somehow still "active" during the nine-month period, patients should have continued losing weight. If, more likely, the drug was cleared from the body, its appetite suppression activity should have abated and modest weight gain would be expected.

9) Treatment with CNTF has resulted in several incidences of *peripheral neuropathies*, although a direct cause-and-effect has not been shown. Specifically, in 1999, Regeneron noted reactivation of herpes simplex virus (cold sores) in patients with prior infections. There has been no mention of this problem in subsequent studies using lower drug dosages. Last February, the company reported one case of Guillain-Barre syndrome in the Axokine arm of the first Phase 3 trial. Finally, Bell's palsy has also been reported in earlier studies. Taken together, the adverse events suggest a finite, but small risk that will only be quantified after broader exposure to Axokine. Recall that the initial product label for Redux included a warning of primary pulmonary hypertension at an incidence of 18 per million. Small risks take on added weight for drugs to be used by potentially large populations.

10) Finally, even if Axokine receives FDA approval, *poor market acceptance* should be expected for a once-a-day injectable that (in Phase 2) resulted in only a ten pound loss in a 250-pound individual after 12 weeks.

The pharmaceutical industry has thrived on serendipity since its earliest days. Valium(Librium) failed in its original indication for hypertension, yet became the imprimatur for all anxiolytics. Likewise, Viagra proved to be an unsatisfactory drug for angina, but succeeded enormously in erectile dysfunction. For both examples, the side-effect became the primary indication. While some biotechnology drugs have found expanded utility beyond their original indication, none have entered the market by targeting a side effect.