

Company: Trimeris, Inc. (TRMS)

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Over the past few weeks, we have worked on a (short) investment thesis in Trimeris, Inc. (TRMS). The project was initiated based on (1) the Company's market capitalization of  $\approx$  \$845 million (\$45.14 with 18.7 million shares on March 21; \$115 million cash, including \$41 million from a January private placement), predicated on (2) expectations of clinical/regulatory success for its first product, T-20, to treat AIDS.

**Conclusion:** *There is sufficient data to support a short position in Trimeris. The Company's clinical development program is highly experimental (risky) and inadequately supported, if at all, by prior clinical trial results. Patient enrollment/treatment criteria in the Company's two Phase 3 trials are substantially different from those employed in a single, small Phase 2 efficacy trial, which failed. Also, with an expected cost of \$12,000 per patient per year (thereby doubling current average annual costs), T-20's potential market could prove significantly smaller than analysts predict. Two mitigating factors to the short thesis are: 1) Due to T-20's novel mechanism of action and minimal toxicity, FDA may experience outside pressure to approve the drug based on very modest results and 2) the AIDS virus in so-called "salvage patients" (as enrolled in both Phase 3 trials) is likely to be resistant to any optimized regimen and, therefore, susceptible to a novel drug like T-20. The first mitigating factor is supported by FDA's October 2001 approval of Gilead's Viread for a broader indication than an advisory Panel recommended. The second factor is purely theoretical.*

Trimeris is expected to release the results from both Phase 3 trials in this half and prior to the 14th International AIDS Conference, which begins July 7. It is likely that the data from each Phase 3 will be released separately (possibly as early as April/May), due to their materiality and the five-week interval between the completion of each trial. In the event of data inadequate for an NDA filing, the stock will likely lose half its value. If the top line data are positive, 20 percent near-term stock price appreciation is possible.

**Introduction:** Founded in January 1993, Durham, North Carolina-based Trimeris was based on the work of its current President/CEO/CSO Dani Bolognesi, Ph.D. and Duke co-researcher Tom Matthews, Ph.D., Senior VP R&D (both co-Founders joined the Company in March and July 1999, respectively). Today, all 16 FDA-approved AIDS drugs are either viral reverse transcriptase inhibitors (RTIs; six are nucleoside-, one is a nucleotide analog and three are non-nucleotide RTIs, so-called NNRTIs) or viral protease inhibitors (PIs; there are six). Trimeris's first potential drug, called T-20 (FKA pentafuside), is a 36-amino acid peptide that targets a different viral protein called GP-41. This protein mediates viral fusion to human immune cells. Once fused, the virus delivers its (ribo)nucleic acid and appropriates the cell's machinery to manufacture more virus (ultimately killing the cell). Thus, T-20 (and the related 39 amino acid peptide, T-1249) are called *fusion inhibitors* and, as such, constitute a new class of AIDS drug.

#### Clinical Trial History:

Trimeris has completed at least nine clinical trials, from its first dose-ranging safety trial begun in 1996 and reported in August 1997 using T-20 as monotherapy (dramatic viral mutation to a resistant strain obviated this approach) to a 450 patient (limit three per physician), open label trial of "deep salvage" patients to test T-20's marketability. Dosages from three to 100 milligrams, delivered intravenously or subcutaneously have been tested. Unfortunately, only two Phase 2 clinical efficacy trials, both small, have been completed. Further, neither of the pivotal Phase 3 trials is directly comparable in design to either Phase 2 study. The Phase 2 trials are summarized below:

206: Initiated February 4, 1999, the plan was to enroll 78 RT or PI (not NNRTI) experienced patients who were placed on a fixed regimen (4-drug; N=19)  $\pm$  T-20, sub-Q, b.i.d. at 50 mg (N=16), 75 mg (N=20) or 100 mg (N=16) with 48wFU; Each T-20 dosage is nominal, since only 90% of drug was deliverable for each injection. Thus, the trial enrolled NNRTI-naive patients, then: To 3 drugs [abacavir (RT) + amprenavir (PI) + ritonavir (PI)] added efavirenz (an NNRTI, DuPont's Sustiva)  $\pm$  T-20. This trial design is essentially testing T-20 (along with Sustiva) as second line therapy.

*Please turn to the next page.*

*Result:* Announced piecemeal at 14dFU, 16wFU (two reports) and 32wFU, a February 24, 2002 abstract (Lalezari et al.) from the 9<sup>th</sup> Conference on Retroviruses and Opportunistic Infections indicated *no statistically significant improvement* in lowering RNA level or increasing CD4+ counts due to T-20 (combined doses) above that afforded by adding Sustiva to the drug regimen. In aggregate, on an intent-to-treat basis, 28 of 51 (55%; 3 doses combined) on T-20 versus 7 of 19 (37%) in the control group had RNA < 400; CD4+ values were higher, 132 with T-20 (combined) versus 90 in controls. Specifically for each of the four arms, 4-drug regimen (RNA down 1.87 Log<sub>10</sub>, CD4+ T-cell up 90); 4-drug regimen plus 50mg T-20 (-2.10 Log<sub>10</sub>, +92), 4-drug plus 75mg T-20 (-2.62 Log<sub>10</sub>, +147) and 4-drug plus 100mg T-20 (-2.39 Log<sub>10</sub>, +124). The study was not powered to test for statistical significance at each dose separately.

'208: Initiated March 14, 2000, this 60 patient (4 cohorts), 48wFU formulation trial was designed to compare two alternative formulations of T-20 at a concentration of 100mg/mL in (1) TRIS buffer (12 patients tested at 100 mg b.i.d.) or (2) carbonate buffer (12 patients tested at 75-, 22 tested at 100 mg b.i.d.) versus the previously employed concentration of 50 mg/mL T-20 in carbonate buffer (tested at 100 mg b.i.d.). The reason for this study is that since 100 mg b.i.d. appeared to be the optimal dosage, two, one-mL subcutaneous injections were required at each administration (four injections per day). Trimeris tested the higher concentration in order to deliver T-20 by a single, one-mL injection, twice a day. Patients were experienced with all three drug types (RT, PI and NNRTI) and entered the trial with CD4+ counts averaging 24 and RNA levels averaging 5.37 Log<sub>10</sub> copies.

*Result:* Data from 46 patients were announced at the same time as '206 above. The TRIS buffer formulation was not successful; however, the pharmacokinetic analysis of T-20 at two-fold higher concentration in carbonate buffer demonstrated bioequivalency to the standard formulation and was subsequently employed in both Phase 3 trials. In aggregate, at 48 weeks, for 23 of 46 patients receiving T-20 (3 drop outs), the median viral RNA dropped from 5.37 log<sub>10</sub> copies/mL to < 400 (limit of detection); CD4 counts rose from a median of 24 to ≈ 140. Specifically (1) patients receiving 100 mg b.i.d. via 100 mg/mL T-20 in carbonate buffer had RNA drop 2.97 Log<sub>10</sub> and CD4+ cells increase by 111 from baseline, (2) patients receiving 75 mg b.i.d. via 100 mg/mL T-20 in carbonate buffer had RNA drop 3.48 Log<sub>10</sub> and CD4+ cells increase by 175 from baseline and (3) patients receiving 100 mg b.i.d. via 100 mg/mL T-20 in TRIS buffer had RNA drop 0.87 Log<sub>10</sub> and CD4+ cells increase by 79 from baseline. Since all patients in the trial received T-20 in one form or another (no control arm), T-20 specific efficacy cannot be gleaned.

In November 2000, Trimeris initiated its first Phase 3 trial of T-20. Study '301 enrolled 525 "deep salvage" (i.e., failed on at least two triple therapy drug regimens over at least a 12 month period) patients at 48 sites in the US, Canada, Mexico and Brazil. Entry criteria included RNA levels above 5,000 copies and patients had their viral infection assessed by genotypic and phenotypic analysis, after which their *drug therapy was optimized*. Patients were then randomized to receive (N=175) optimized background regimen ± 100 mg T-20 b.i.d. (N=350) via one, subcutaneous injection each time. The PCE evaluated at 24wFU is 0.5-1.0 log<sub>10</sub> lower viral load in a 48 week study. Enrollment of the last patient was completed on June 28, 2001 implying that this patient's final analysis would be done by December 13, 2001 (24 weeks).

A near identical study, '302, with very slightly different entry criteria, began in January 2001 and took place in Europe and Australia. Enrollment of the last patient was completed on August 8, 2001 implying that this patient's final analysis would be done by January 23, 2002.

Note that both Phase 3 trials (1) use a T-20 formulation that has not been tested in a "no T-20" controlled trial and (2) are enrolling patients in deep salvage receiving an optimized drug regimen.

### Corporate Partnership

Part of Trimeris' valuation is supported by a corporate partnership with Hoffmann-LaRoche. Roche has worldwide rights to T-20 (and second generation T-1249 which is 2-3 years behind T-20), splits North American revenues 50/50 with Trimeris and is expected to pay a 10-12 percent royalty on ROW revenues. While Roche is a respected partner (with a modest AIDS

portfolio), its most significant contribution lies in its T-20 manufacturing capabilities. The synthesis of a 36 amino acid peptide, used at  $\approx 75$  grams per patient per year, would require the largest peptide facility in the world. For comparison, a patient using Amylin's similarly sized, daily dosed peptide called Symlin would need  $\approx 70$  milligrams per year, a thousand-fold less peptide. The scale required to manufacture T-20 is without precedent.

Events: There are two events relevant to TRMS within the next three months.

1. *Top-line '301 Data;* Release is possible as early as late April or May. The last patient would have been treated and would have completed their 24wFU by December 13, 2001. Data are being collected from the U.S., Canada, Mexico and Brazil, a complicated scenario at best; however, these data will be viewed as crucial to FDA approval.
2. *Top-line '302 Data;* Release is likely to follow '301 by about five weeks, since the last patient would have been treated and would have completed their 24wFU by January 23, 2002. Data from Europe and Australia will support and may be sufficient for CE mark (European Medicines Evaluation Agency approval). Results from '302 discordant with '301 would likely prevent FDA approval given the two trials' near identical design.