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10 UNITED STATES DISTRICT COURT
11 NORTHERN DISTRICT OF CALIFORNIA

12 In re CV THERAPEUTICS, INC.
13 SECURITIES LITIGATION

) No.
) C-03-3709-SI

14 _____
15 This Document Relates To:
16 ALL ACTIONS.

) CLASS ACTION
) CONSOLIDATED COMPLAINT FOR
) VIOLATION OF THE FEDERAL
) SECURITIES LAWS

17 DEMAND FOR JURY TRIAL
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1 **SUMMARY AND OVERVIEW**

2 1. This is a securities class action on behalf of all purchasers of the publicly-traded
3 securities of CV Therapeutics, Inc. (“CV Therapeutics” or the “Company”) between December 30,
4 2002 and December 5, 2003 (the “Class Period”), against CV Therapeutics and certain of its officers
5 and directors for violations of the Securities Exchange Act of 1934 (the “1934 Act”). Plaintiff
6 alleges that the fraud is ongoing and, if successful, could lead to the death of many.

7 2. CV Therapeutics is a biopharmaceutical company focused on the discovery,
8 development and commercialization of new small molecule drugs for the treatment of cardiovascular
9 diseases. To date, the Company has not received approval from the Food and Drug Administration
10 (“FDA”) for any of its drugs. Only one of the Company’s drugs – Ranexa, for the treatment of
11 chronic angina – has even reached the stage of being considered for FDA approval. Thus, the
12 Company is relying on the approval of this drug as its claim to fame.

13 3. Throughout the Class Period, defendants misled analysts, the investing public and
14 even the FDA into believing that their novel anti-anginal drug, Ranexa, was safe and effective for
15 public use in an unrestricted population, and that the Company had conducted sufficient clinical
16 studies to prove it. For example, the Company dismissed the widely-publicized concern that Ranexa
17 caused QT prolongation (“QT”), a dangerous form of heart rhythm irregularity, characterized as a
18 significant gap in time between heartbeats.

19 4. According to the FDA, QT prolongation of over 10-20 milliseconds (“msec”) is a
20 concern. A prolongation of over 20 msec is dangerous. In addition, an interval (QT) of over 500
21 msec was seen as “extreme” and “troublesome property.” Yet, unknown to the investing public, the
22 data submitted by CV Therapeutics pertaining to QT prolongation for Ranexa in support of its New
23 Drug Application (“NDA”) fell within these parameters. The result of these false and misleading
24 statements was the artificially inflated stock price of CV Therapeutics.

25 5. Further, during the Class Period, defendants issued a series of false and/or misleading
26 statements in order to mislead the investing public into believing that Ranexa was closer to being
27 approved by the FDA than it really was. In July 2003, defendants misrepresented that the FDA had,
28 in fact, scheduled Ranexa to be reviewed by the FDA Cardiovascular-Renal (“Cardio-Renal”)

1 Advisory Committee (“Advisory Committee”) on September 15-16, 2003, an event which signifies
2 that the FDA is ready to act on the drug. Internal FDA notes, however, reveal that, in fact, there was
3 little likelihood that such a meeting could take place, because the data submitted by CV Therapeutics
4 was incomplete. The result of these false or misleading statements was to artificially inflate the price
5 of CV Therapeutics’ stock. When, on August 1, 2003, the Company was forced to admit that this
6 alleged meeting was “cancelled,” the stock took the first of a series of nose-dives, plunging 20.8%,
7 falling \$7.31 to close at \$27.87 per share.

8 6. On October 23, 2003, the Company announced that the FDA Advisory Committee
9 was reviewing Ranexa on December 9, 2003. On that news, the stock partially recovered, jumping
10 from \$18.22 per share on October 22, 2003 to \$22.45 per share on October 23, 2003.

11 7. However, this rise was short-lived, for on October 30, 2003, the FDA issued an
12 “approvable letter with conditions” indicating that “additional clinical information is needed prior to
13 approval.” Exhibit (“Ex.”) 2¹. (*Bioworld Today*, Nov. 3, 2003). Notably, “[t]he FDA’s concerns
14 center around the product’s risk-benefit profile, relative to QTc prolongation that occurs in patients
15 using the therapeutic.” *Id.* Defendants, however, repeatedly had denied that QT prolongation would
16 cause delay of Ranexa’s approval. On this news, the stock took its second significant drop during
17 the Class Period, falling 21.7%, losing \$4.89, and closing at \$17.63 per share.

18 8. Defendants, however, continued to represent that they had no concern about Ranexa’s
19 clinical studies, stating: “This is an approvable letter, so it tells us that there are multiple paths to an
20 approval.” *Id.* (quoting John Bluth, CV Therapeutics’ Director of Corporate Communications).

21 9. On the eve of the December 9, 2003 FDA Advisory Committee hearing, the FDA
22 released internal documents in connection with its review of the Company’s Ranexa NDA, including
23 the October 30, 2003 Approvable Letter (“Approvable Letter”). Ex. 3. These documents reveal that
24 the FDA found major deficiencies pertaining to the Company’s clinical studies, including the QT
25 prolongation, the efficacy in women, and the fact that 98% of the study population was Caucasian.

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27 ¹ With the exception of Ex. 1, which is appended directly hereto, Exs. 2-49 have been filed
28 concurrently herewith in a separate Appendix of Exhibits.

1 Ex. 4 (Clinical Review). In the briefing to the FDA Advisory Committee, John Koerner of the
2 FDA's Cardio-Renal drug products division stated that CV Therapeutics "ha[s] failed to prove that
3 QT prolongation – a delay in the time it takes the heart to electrically recharge itself – is not a
4 concern." Exs. 5 and 6 (*American Health Line*, Dec. 11, 2003; *The Wall Street Journal*, Dec. 10,
5 2003). Also revealed for the first time was:

- 6 • The fact that the FDA had previously sent defendants a Discipline Letter outlining
7 severe deficiencies in the NDA, prompting defendants to file an amendment.
- 8 • The fact that the FDA had encouraged CV Therapeutics, because of the QT
9 prolongation dangers, to do a second-line therapy study of resistant angina patients as
10 a possible group for whom Ranexa could be approved.
- 11 • The fact that the "Approvable Letter" received by defendants in late October 2003
12 strongly criticized the NDA, and raised serious efficacy and safety concerns
13 requiring more studies. The drug did not appear to work in women, and caused large
14 QT effects on certain populations such as those with hepatic impairment. The letter
15 concluded "given the availability of other anti-anginal drugs that do not prolong the
16 QT interval, there needs to be a clear reason to approve a therapy with what appears
17 to be additional, possibly life-threatening risk."

18 10. Upon the release of the FDA internal documents, on December 8, 2003, the stock
19 took another plunge, dropping 27% to \$12.21 per share.

20 11. In response to this news, analysts slashed their estimates for the Company:

21 (a) On December 10, 2003, Deutsche Bank Securities Inc. ("Deutsche Bank")
22 downgraded its rating from Buy to Hold, reducing its estimates from \$43 to \$14, stating, "[d]ue to
23 this decision and the requirements for additional studies, we have delayed our Ranexa launch
24 estimate by two years." Ex. 7 (Deutsche Bank, Dec. 10, 2003).

25 (b) On December 10, 2003, Bear, Stearns & Co. Inc. ("Bear Stearns") estimated
26 that Ranexa would not be approved (if approved at all) until at least 2006, and therefore,
27 downgraded CV Therapeutics from Peer Perform to Underperform based on the FDA and Advisory
28 Committee's request for additional clinical studies. Ex. 8 (Bear, Sterns, Dec. 10, 2003).

(c) According to Thomas Wei of USBancorp Piper Jaffray ("USBancorp"), in his
December 2, 2003 report, for "[d]rugs that received approvable letters but were delayed due to FDA
requests for additional clinical data," the result is that the mean total approval time from NDA filing
is 34 months. Similarly, for "[d]rugs that received approvable letters but were delayed due to FDA

1 concerns related to QTc prolongation,” the mean total approval time from the filing of the NDA is
2 32 months. Ex. 9 (USBancorp, Dec. 2, 2003).

3 12. As a result, Dr. Levy of White Mountain Capital, LLC (“White Mountain Capital”),
4 an independent analyst, wrote in a comment published to his clients on December 12, 2003:

5 [T]he company should also be taken to task for its insistence on applying for
6 approval in an unrestricted population, as well as its *incomplete (and misleading)*
disclosure of information to the investment community.

7 Ex. 10 (White Mountain Capital, Dec. 12, 2003).

8 13. *The New York Times* commented on the recent trend of biotechnology companies’
9 misleading statements coming to light on the eve of FDA Advisory Committee hearings. *The New*
10 *York Times* December 26, 2003 article refers to CV Therapeutics as one such company, stating:

11 But on some occasions, when a drug is considered by an F.D.A advisory
12 panel, for instance, documents are released outlining the F.D.A.’s views. And it
sometimes turns out the company’s picture was *rosier than reality*.

13 * * *

14 Another recent case that *has raised* some eyebrows is that of *CV*
15 *Therapeutics Inc.* of Palo Alto, Calif., which is developing a drug to treat angina, the
chest pain that can precede heart attacks.

16 This month, in connection with an advisory panel meeting, the F.D.A. made
17 public a letter it had sent to the company. The letter said that while the drug, Ranexa,
18 showed evidence of effectiveness, there were “three important safety concerns” that
19 had to be addressed with more studies before the drug could be approved. The drug
had impaired fertility in rats, had shown signs that it might cause heart rhythm
irregularities in people and had not been tested on enough people to establish its
safety, the agency said.

20 When it received the letter in October, CV issued a news release. It described
21 the letter’s contents this way: “The F.D.A. indicated that there is evidence that
22 Ranexa is an effective anti-anginal this way, and that additional clinical information
is needed prior to approval.”

23 John Bluth, a spokesman for CV said yesterday, “We absolutely believe the
disclosure was complete.”

24 Ex. 11, (*The New York Times*, Dec. 26, 2003).

25 14. The true facts, which were known by each of the defendants during the Class Period,
26 but were concealed from the investing public, included the following:

27 (a) That CV Therapeutics’s announcement on July 7, 2003 of a scheduled
28 Advisory Committee meeting for Ranexa was misleading because neither the FDA nor CV

1 Therapeutics had in fact yet decided to go ahead with a September 2003 Advisory Committee
2 meeting for Ranexa because of severe deficiencies in the NDA. Questions by the FDA needed to be
3 resolved prior to any such meeting. In fact, defendants knew that at most the schedule was merely a
4 “place holder;”

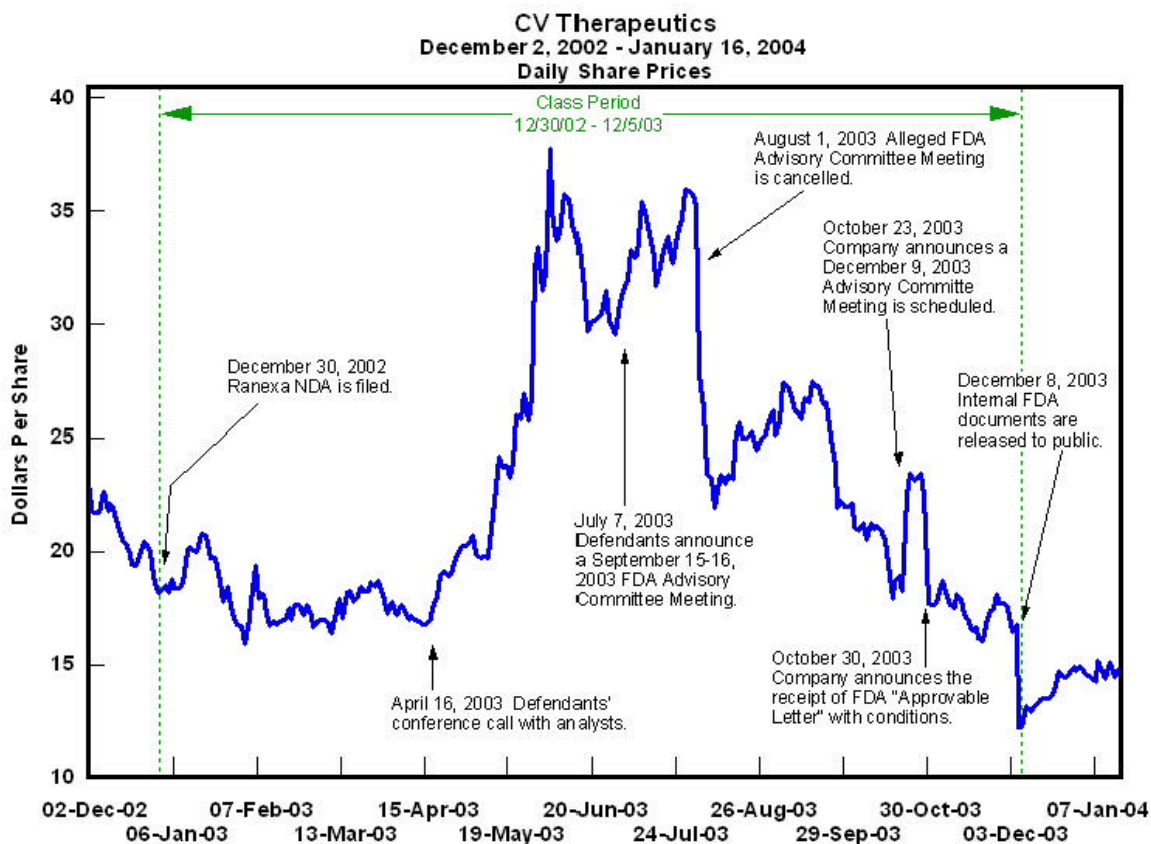
5 (b) The Company was aware that its data regarding its findings of QT interval
6 prolongation posed serious concerns and had been portrayed in a misleading fashion to the investing
7 public;

8 (c) Because of the serious safety concerns regarding QT/QTc prolongation
9 limiting chances of approval for the drug, the FDA had encouraged CV Therapeutics to study the
10 drug as a second-line therapy; and

11 (d) That the safety and efficacy data of Ranexa were so flawed and deficient that
12 the NDA for Ranexa would not be approved without additional clinical trials.

13 15. The following chart graphically demonstrates the effect of CV Therapeutics’
14 statements on the market:

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JURISDICTION AND VENUE

16. Jurisdiction is conferred by §27 of the 1934 Act. The claims asserted herein arise under §§10(b) and 20(a) of the 1934 Act and Rule 10b-5 promulgated thereunder.

(a) Venue is proper in this District pursuant to §27 of the 1934 Act. Many of the false and misleading statements were made in or issued from this District.

(b) The Company's principal executive offices are in Palo Alto, California, where the day-to-day operations of the Company are directed and managed.

THE PARTIES

17. Plaintiff David Crossen purchased CV Therapeutics publicly-traded securities as described in the certification previously filed with the Court and was damaged thereby. Crossen was appointed lead plaintiff on November 21, 2003.

1 18. Defendant CV Therapeutics is a biopharmaceutical company focused on the
2 discovery, development and commercialization of new small molecule drugs for the treatment of
3 cardiovascular diseases.

4 19. In August 2000, CV Therapeutics entered into a financing agreement with Acqua
5 Wellington North American Equities Fund, Ltd. (“Acqua Wellington”) for the purchase of CV
6 Therapeutics common stock. Under this agreement, CV Therapeutics, in its sole discretion, could
7 present Acqua Wellington with draw-down notices, pursuant to which Acqua Wellington was
8 required to purchase the common stock for specified total proceeds over a specified pricing period.
9 In accordance with this “equity line of credit,” on January 29, 2003, CV Therapeutics sold stock to
10 Acqua Wellington for proceeds of \$6.9 million. The Company also sold stock to Acqua Wellington
11 on March 24, 2003 for proceeds of \$11.8 million and again on September 16, 2003 for
12 approximately \$14.9 million. On June 12, 2003, CV Therapeutics announced that it was issuing
13 \$100 million aggregate principal amount of senior subordinated convertible debentures. On October
14 3, 2003, CV Therapeutics filed a mixed-shelf registration statement for \$300 million of debt
15 securities. The Company has not, however, issued any securities according thereto.

16 20. Defendant Louis G. Lange (“Lange”) was a founder of the Company and the
17 Chairman and Chief Executive Officer (“CEO”) of CV Therapeutics. He signed all of the
18 Company’s SEC filings during the Class Period. In the years 2000, 2001 and 2002 Lange received
19 salaries of \$311,250, \$350,000 and \$425,000, respectively, bonuses of \$115,000, \$400,000 and
20 \$425,000, respectively, and loan forgiveness of \$113,750, \$53,750 and \$43,750, respectively.
21 During the Class Period, Lange sold 30,000 of his CV Therapeutics shares for proceeds of
22 \$765,055.50.

23 21. Defendant Brent K. Blackburn (“Blackburn”) was a Senior Vice President of Drug
24 Discovery and Pre-Clinical Development for CV Therapeutics who reported directly to Lange. In
25 the years 2000, 2001 and 2002 Blackburn received salaries of \$240,000, \$212,000 and \$183,750,
26 respectively, bonuses of \$110,000, \$100,000 and \$80,000, respectively, and loan forgiveness of
27 \$8,000, \$8,000 and \$8,000, respectively. During the Class Period, Blackburn sold 9,710 of his CV
28 Therapeutics shares for proceeds of \$301,170.90.

1 22. Defendant Daniel K. Speigelman (“Speigelman”) was a Senior Vice President and the
2 Chief Financial Officer (“CFO”) of CV Therapeutics. He signed the SEC Reports on Form 10-K
3 and 10-Q filed during the Class Period and reported directly to Lange. In the years 2000, 2001 and
4 2002 Speigelman received salaries of \$252,500, \$240,000 and \$220,000, respectively, bonuses of
5 \$100,000, \$80,000 and \$80,000, respectively, and loan forgiveness of \$10,000, \$10,000 and
6 \$10,000, respectively. During the Class Period, Speigelman sold 11,000 of his CV Therapeutics
7 shares for proceeds of \$286,972.20.

8 23. Defendant Luiz Belardinelli (“Belardinelli”) was a Vice President of Drug Research
9 and Pharmacologic Sciences for CV Therapeutics who reported directly to Blackburn.

10 24. The individuals named as defendants in ¶¶20-23 are referred to herein as the
11 “Individual Defendants.” The Individual Defendants, because of their positions with the Company,
12 possessed the power and authority to control the contents of CV Therapeutics’ quarterly reports,
13 press releases and presentations to securities analysts, money and portfolio managers and
14 institutional investors, *i.e.*, the market. Because of their positions, each defendant was likely
15 provided with copies of the Company’s reports and press releases alleged herein to be misleading
16 prior to or shortly after their issuance and had the ability and opportunity to prevent their issuance or
17 cause them to be corrected. Because of their positions and access to material non-public information
18 available to them but not to the public, each of these defendants likely knew that the adverse facts
19 specified herein had not been disclosed to and were being concealed from the public and that the
20 positive representations which were being made were then materially false and misleading. The
21 Individual Defendants are liable for the false statements plead herein at ¶¶87-91, 93-96, 99-101, 105,
22 107, 109, 112-116, as those statements were each “group-published” information, the result of the
23 collective actions of the Individual Defendants.

24 **FRAUDULENT SCHEME AND COURSE OF BUSINESS**

25 25. Each defendant is liable for (i) making false statements, *or* (ii) failing to disclose
26 adverse facts known to him about CV Therapeutics. Defendants’ fraudulent scheme and course of
27 business that operated as a fraud or deceit on purchasers of CV Therapeutics’ publicly-traded
28 securities was a success, as it (i) deceived the investing public regarding CV Therapeutics’ prospects

1 and business; (ii) artificially inflated the prices of CV Therapeutics' publicly-traded securities; (iii)
2 allowed defendants to arrange to sell and actually sell in excess of \$132 million worth of CV
3 Therapeutics securities at artificially inflated prices; (iv) allowed several defendants to sell their own
4 shares at artificially inflated prices; and (v) caused plaintiff and other members of the Class to
5 purchase CV Therapeutics publicly-traded securities at inflated prices.

6 **BACKGROUND AND OVERVIEW**

7 **About CV Therapeutics**

8 26. The Company was incorporated in Delaware in December 1990 and changed its name
9 to CV Therapeutics, Inc. in June 1992. Since its inception, the Company has been engaged in
10 research and development activities and has generated no product revenues. The Company has
11 financed its operations primarily through the sale of preferred equity securities, equipment and
12 leasehold improvement financing and other debt and equity financing.

13 27. The Company is a biopharmaceutical company focused exclusively on the application
14 of molecular cardiology to the discovery, development and commercialization of novel, small
15 molecule drugs for the treatment of chronic cardiovascular diseases. The Company claims that
16 molecular cardiology was developed, in part, by CV Therapeutic scientists and their academic
17 collaborators and is based upon the application of molecular biology and genetics to cardiovascular
18 diseases. This discipline has yielded new insights into the mechanisms underlying chronic
19 cardiovascular diseases and has enhanced the search for innovative cardiovascular drugs by
20 providing an increasing number of new molecular targets for drug discovery. To date, CV
21 Therapeutics claims to have discovered several compounds and completed the strategic in-license of
22 a sixth compound for treatment of chronic cardiovascular diseases-Ranolazine/Ranexa.

23 28. Ranolazine is a patented compound which was tested in the early 1990's by Syntex,
24 (U.S.A.), Inc. ("Syntex"), an indirect subsidiary of Roche Holding Limited ("Roche") in Phase I and
25 Phase II trials in patients with angina. It fits the Company's criteria for development candidates as it
26 is a small molecule which works through a novel mechanism of action. CV Therapeutics obtained a
27 license for ranolazine from Syntex in March 1996, after the acquisition of Syntex by Roche. The
28 Company, along with the hiring of Dr. Andrew A. Wolff, Senior Vice President, Clinical Research

1 and Development, from Syntex in 1994, began developing ranolazine to treat angina because the
2 Company claimed to believe it did not impair blood pressure or heart rate and had an improved
3 tolerability profile. Dr. Wolff had previously served from June 1993 until September 1994 as the
4 Executive Director of Medical Research and New Molecules Clinical Programs Leader for Syntex.

5 29. Ranolazine acts by modulating the body's metabolism to shift the source of energy
6 for the heart from fatty acid toward glucose. Ranolazine decreases the heart's oxygen demand for a
7 given level of cardiac work because less oxygen is required to produce an equivalent amount of
8 energy from glucose than from fatty acids.

9 30. The Company's NDA for Ranexa (ranolazine) for the treatment of chronic angina
10 was filed with the FDA on December 30, 2002 and accepted by the FDA for review on March 5,
11 2003. Ranexa belongs to a new class of compounds that partially inhibit fatty acid oxidation. If
12 approved by the FDA, Ranexa would represent the first new class of anti-anginal therapy in the
13 United States in more than 20 years.

14 31. CV Therapeutics currently has no drugs on the market. Ranexa is the Company's
15 "claim to fame" and is the only one of the Company's "product candidates" to have reached the
16 stage of submission of an NDA. The remainder of the Company's products are either in clinical
17 trials under an Investigational New Drug application ("IND") or applicable foreign regulatory
18 authority submission, or in preclinical research and development. The success of the Company,
19 therefore, turns on the approval of Ranexa.

20 32. Chronic angina is marked by repeated and sometimes unpredictable attacks of cardiac
21 pain. Angina attacks occur when the heart is not receiving all the oxygen it requires to function
22 effectively. These attacks are typically triggered by physical exertion or emotional stress. Usually
23 angina is associated with coronary artery disease, which is characterized by a buildup of fatty
24 plaques in coronary arteries that reduce the flow of oxygen-rich blood through the heart. According
25 to the American Heart Association, 6.6 million people in the United States have angina and 400,000
26 new cases are diagnosed each year.

27 33. At all times during the Class Period, the Ranexa NDA was defendants' only
28 marketing application for any of their drugs in development. Defendants do not have any other

1 products in the marketplace. The success of the Ranexa NDA is thus critical to the continued
2 success of the Company.

3 **Ranexa and Potential for QT/QTc Cardiac Side Effects**

4 34. Ranexa is an anti-anginal therapy drug, known to extend the QT interval. Adverse
5 pro-arrhythmic effects linked to QT interval prolongation are of concern to the FDA. Side effects
6 linked to QT interval prolongation include torsade de pointes, ventricular tachycardia, ventricular
7 arrhythmia, ventricular ectopy, ventricular fibrillation and flutter, cardiac arrest, sudden death,
8 syncope, dizziness and palpitations.

9 35. Torsade de pointes is a syndrome of polymorphic ventricular tachycardia occurring in
10 the setting of marked prolongation of the electrocardiographic QT interval. It occurs in individuals
11 genetically predisposed to the disorder and is a frequent cause of sudden death in these individuals.
12 More importantly and of particular concern in the design and study of new cardiovascular drug
13 products, torsade de pointes can also occur as a complication of those drugs that prolong the QT
14 interval by blocking potassium channels.

15 **Relevance of QT/QTc to the FDA and the Investing Public**

16 36. QT interval prolongation is not a new or novel issue. It has been one of the FDA's
17 primary focal points in analyzing the safety of drugs in development. In fact, "[r]ecent drug
18 withdrawals, denials and filing delays have been attributed to [the] drugs' effects on the QTc
19 interval." Ex. 12 (Deutsche Bank, Oct. 27, 2003).

20 37. On May 23, 2001, Douglas C. Throckmorton, Director of the Division of Cardio-
21 Renal Drug Products defined the FDA's position regarding cardiovascular drugs that prolong the QT
22 interval. The FDA advised that: (a) the use of cardiovascular drugs that prolong the mean QT in a
23 dose-dependent fashion is associated with an increased risk for torsade de pointes and sudden death;
24 (b) the approval of cardiac drugs requires demonstration of symptomatic benefit, sufficient
25 description of the arrhythmic risk (drug effect over a broad dose range, exploration of factors that
26 modify the arrhythmic risk and point estimates of total mortality in the high risk and target
27 populations); and (c) *where cardiac drug approval is sought as a second-line therapy, there must*
28

1 *be a demonstration of a symptomatic benefit in a resistant population.* Ex. 13 (Cardiovascular
2 *Drugs That Prolong the QT Interval*, May 23, 2001, Powerpoint).

3 38. On February 7, 2002, the FDA, in conjunction with the “International Conference on
4 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use,”
5 (“ICH”) issued its draft consensus guideline entitled, “Safety Pharmacology Studies for Assessing
6 the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human
7 Pharmaceuticals, §S7B.” Ex. 14. These guidelines provide that in analyzing the QT prolongation
8 effects of a drug, *non-clinical, as well as clinical*, data should be observed. Among the data to be
9 analyzed is ECG data. *Id.*

10 39. On November 15, 2002, the FDA published a preliminary concept paper entitled “The
11 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-
12 Antiarrhythmic Drugs.” Ex. 15 (“Concept Paper”). The FDA guidance, which was known by
13 defendants, is as follows for Ranexa, which was viewed principally as non-antiarrhythmic:

14 Substantial prolongation of the QT/QTc interval, with or without documented
15 arrhythmias, *may be the basis for non-approval* of a drug or discontinuation of its
16 clinical development, *particularly when the drug has no clear advantage over*
17 *available therapy* and available therapy appears to meet the needs of most patients.
Failure to perform an adequate non-clinical and clinical assessment of the potential
QT/QTc interval prolonging properties of a drug may likewise be justification to
delay or deny marketing authorization.

18 Special considerations apply to anti-arrhythmic drugs that utilize delayed
19 repolarization as part of their mechanisms, but in this case, it will be critical to
20 provide outcome data to quantify risk. Whether such a drug could be approved would
depend on the nature of its benefit, the size of its effect on the QT/QTc interval, and
the potential for managing or reducing risk by dose limitation, monitoring, or other
approaches.

21 *For non-antiarrhythmic drugs*, the outcome of the risk benefit assessment
22 will be influenced by *the size of the QT/QTc interval prolongation effect*, whether
the effect occurs in most patients or only in certain defined outliers, *the overall*
23 *benefit* of the drug, and the utility and *feasibility of risk management options*. The
24 inclusion of precautionary material in the prescribing information will not necessarily
represent an adequate risk management strategy, if implementation of the
recommendations in a clinical use setting is judged to be unlikely.

25 If QT/QTc interval prolongation is a feature shared by other drugs of the
26 therapeutic class in question, evaluation of the new drug will involve a comparison of
the magnitude and incidence of any QT/QTc interval prolongation effects relative to
27 those of other members of its class in concurrent active control groups. An excess
risk for the new drug relative to approved therapies would, other things being equal,
28 have a negative impact on its risk-benefit assessment.

1 For drugs that prolong the QT/QTc interval, the mean degree of prolongation
2 has been roughly correlated with the observed risk of clinical proarrhythmic events.
3 Whether there are drugs that cause *extreme prolongation (e.g., >500 msec) in a
small fraction of patients with only modest mean effects is not clear, but this would
seem to be a troublesome property.*

4 *It is difficult to determine whether there is an effect on the mean QT/QTc
interval that is so small as to be inconsequential, although drugs whose maximum
5 effect is less than 5 msec at high doses and during co-administration of saturating
doses of metabolic inhibitors, have not so far been associated with torsade de pointes.
6 Whether this signifies that no increased risk exists for these compounds or simply
that the increased risk has been too small to detect is not clear.* To date, drugs that
7 prolong the mean QT/QTc interval by 5-10 msec under conditions of maximum
effect have also not been clearly associated with risk. *Drugs causing a mean 10-20
8 msec increase under conditions of maximum effect are of concern, but have been
approved if they appear to have important therapeutic roles. Drugs that prolong the
9 mean QT/QTc interval by >20 msec have a substantially increased likelihood of
being proarrhythmic, and may have clinical arrhythmic events captured during drug
10 development. While it has been suggested that some drugs might prolong the
QT/QTc interval up to a "plateau" value, above which there is no dose-dependent
11 increase, this has not been demonstrated adequately to date. As noted, it is critical to
identify the "worst case scenario," i.e., the QT/QTc interval measured in the target
12 patient population at the time of peak effect and under conditions of the highest
blood levels that can be attained during therapy as a result, e.g., of a drug-drug
13 interaction.*

14 *Regardless of the degree to which a drug prolongs the QT/QTc interval,
decisions about its development and approval will depend upon the morbidity and
15 mortality associated with the untreated disease or disorder and the demonstrated
clinical benefits of the drug, especially as they compare with available therapeutic
16 modalities. Demonstrated benefits of the drug in resistant populations or in
patients who are intolerant of approved drugs for the same disease represent
17 additional relevant clinical considerations that might justify approval of the drug,
if the indication were limited to use in such patients.*

18 Ex. 15 at 20-22 (Concept Paper).

19 40. In general, the November 15, 2002 Concept Paper provided guidance on: (a) clinical
20 trial designs for assessment of QT prolongation; (b) approaches to the statistical correction of QT
21 interval for drugs that increase heart rate; and (c) risks of cardiac arrhythmia associated with
22 different degrees of QT prolongation. The approach advocated by the FDA requires a significantly
23 more sophisticated analysis of ECG data.

24 41. Consistent with these standards pertaining to QTc data, analysts following biotech
25 companies have guided the public to rely on these standards in assessing the prospects of a drug for
26 approval:
27

1 To fully evaluate the regulatory risk associated with QTc prolongation,
2 investors should arm themselves with the following data on any new drug in
development.... *The proportion of patients with QTc intervals over 500 msec....*

3 However, based on comments made at the Geodon [advisory committee]
4 panel meeting, we believe that the Cardio-Renal Drugs division will be hesitant to
unrestrictedly approve drugs that cause QTc prolongation beyond 20 msec or have
5 *any significant incidence of patients with QTc intervals over 500 msec.*

6 Ex. 12 (Dennis Harp, Deutsche Bank, Oct. 27, 2003).

7 QTc *measurements greater than 500 msec* have also been *a source of*
8 *concern* for regulators, based on the assumption that measurements greater than 440
msec define prolonged QTc.

9 Ex. 16 (Matt Geller, Ph.D., CIBC World Markets, Oct. 20, 2003).

10 **Approvable and Discipline Review Letters**

11 42. Important to the investment community is the issuance of letters by the FDA in
12 response to the filing of the NDA.

13 43. In a November 1997 letter to Congress regarding the reauthorization of the
14 Prescription Drug User Fee Act (PDUFA) as part of the Food and Drug Administration
15 Modernization Act of 1997, the Secretary of Health and Human Services committed the FDA to
16 certain user fee performance goals and additional procedures related to the review of PDUFA
17 products. These include the goals of reviewing and acting on increasing percentages of applicants'
18 original new drug applications (NDAs) or biologics license applications (“BLAs”), within 6 months
19 for priority applications and within *10 months for standard applications for drugs and biologics*.
20 The term “review” and “act” on means the issuance of an action letter after the complete review of a
21 filed application. In addition to the performance goals for application review, to help expedite the
22 development of drugs and biologics, the Secretary specified that the FDA intends to provide early
23 Agency thoughts on possible deficiencies to applicants in a letter as each discipline finishes its initial
24 review of its portion of the pending application (except when it results in the ability to issue an
25 action letter).

26 44. Upon implementation of PDUFA 1, the Center for Biologics Evaluation and Research
27 (CBER) and the Center for Drug Evaluation and Research (CDER) undertook to review and act on
28 complete NDAs and BLAs within agreed upon time frames. As part of this undertaking the FDA

1 instituted the use of two types of letters – action letters and IR letters. The FDA issued an ***action***
2 ***letter (not approvable, approvable or approval letter)*** after a complete review of the application. ***If***
3 ***not an approval, the action letter contained a complete list of deficiencies in the application and***
4 ***completed the review cycle for the application.*** The next review cycle (resubmission) began when
5 the agency received a complete response to all deficiencies listed in the letter. CDER and CBER
6 used IR letters to ask for information that would assist reviewers during the course of the review or
7 to convey deficiencies identified in the application in advance of the issuance of an action letter.
8 These IR letters did not stop the review clock, did not signal the completion of a review cycle, and
9 were not used consistently across divisions or centers.

10 45. In discussions held to prepare for the reauthorization of PDUFA (PDUFA 2), the
11 industry proposed that applicants be ***notified of any deficiencies*** in an NDA as early as possible after
12 a discipline review had been completed. It was agreed that deficiencies would be communicated in a
13 specific type of letter. The company could then begin preparing a response to the deficiencies,
14 thereby decreasing the response time to the Agency and potentially expediting availability of
15 products to consumers. Although the enclosure to the PDUFA 2 goals letter signed by Secretary
16 Shalala refers to these as IR letters, ***the FDA found that it was less confusing if these letters are***
17 ***clearly identified as a unique type of letter – the discipline review letter (“DR letter”).***
18 Consequently, the Agency will continue to use an IR letter, if needed, to request information while a
19 specific discipline review is in progress and institute the use of a ***DR letter to convey early thoughts***
20 ***on possible deficiencies in the discipline's section of the application when a discipline review is***
21 ***complete.***

22 46. A discipline review refers to the review of sections of the NDA by staff with that
23 expertise. These sections include, but are not limited to, the clinical section, the chemistry,
24 manufacturing and controls section, the non-clinical pharmacology and toxicology section, and the
25 human pharmacokinetics and bioavailability section. As part of their PDUFA 2 commitments at the
26 conclusion of a discipline review, CBER and CDER will send a discipline review letter to the
27 applicant identifying deficiencies in that particular discipline's portion of an application as described
28 in this document, unless the discipline review completes the review of the application.

1 47. An action letter is a letter to an applicant that is issued after the complete review of a
2 filed application. If the letter is not an approval letter, it will set forth in detail the specific
3 deficiencies and, where appropriate, the actions necessary to place the application in condition for
4 approval. An action letter may contain additional or fewer deficiencies than were provided in
5 previously issued DR letters, depending on the final review of the application and supervisory
6 evaluation by Division and/or Office Directors. The issuance of an action letter completes the
7 review cycle for a pending application. It is the benchmark by which the Agency's performance
8 against the PDUFA application review goals is measured.

9 48. A *discipline review letter*, or DR letter, is a letter used to convey *early thoughts on*
10 *possible deficiencies found by a discipline review team for its portion of the pending application at*
11 *the conclusion of the discipline review*. The FDA does not consider DR letters to be action letters
12 because they do not represent a complete review of the submission and, therefore, do not stop the
13 user fee review clock. In addition, a DR letter does not necessarily reflect input from upper
14 supervisory levels (*i.e.*, Division or Office Directors). A single DR letter may contain comments
15 from multiple discipline reviews if it is more efficient to do so. The FDA may review such
16 information if it determines that such review would not adversely affect its ability to meet its
17 PDUFA performance goal for that review cycle. *The FDA has no obligation to review information*
18 *submitted in response to a DR letter during the review cycle in which the DR letter was issued.*

19 **Significance of the FDA Review Process and Advisory Board Meetings to the Market**

20 49. Often, once a drug has been reviewed by the FDA, the FDA will convene an
21 Advisory Committee for its input, prior to approval. This is an important step to the investment
22 community as it indicates progress towards approval. While the FDA ultimately does not have to
23 follow the recommendations of the Advisory Committee, it is rare for them not to follow the
24 Committee's recommendations.

25 **SCIENTER**

26 **A. Motive**

27 50. Defendants were motivated to perpetrate this fraud in order to ensure the approval of
28 Ranexa. CV Therapeutics currently has no drugs in the market. Ranexa is the most advanced drug

1 in the CV Therapeutics product pipeline, and the only drug for which the Company has submitted an
2 NDA for FDA review. The Company's survival depends upon the approval of Ranexa.

3 51. Defendants were further motivated to commit fraud in order to maintain an inflated
4 stock value and raise cash. On August 7, 2000, CV Therapeutics had entered into an "Amended and
5 Restated Common Stock Purchase Agreement." Under this "equity line of credit" agreement, CV
6 Therapeutics was entitled to sell a total of \$149.0 million of its common stock to Acqua Wellington
7 through December 2003. The purchase agreement provided that from time to time, in the sole
8 discretion of CV Therapeutics, the Company could present Acqua Wellington with draw-down
9 notices constituting offers to sell CV Therapeutics common stock for specified total proceeds over a
10 specified pricing period. Once presented with a draw-down notice, Acqua Wellington was required
11 to purchase a pro rata portion of shares of CV Therapeutics common stock as allocated on each
12 trading day *during the pricing period* (18 consecutive trading days following a draw-down notice)
13 on which the daily volume weighted average price for its common stock exceeded a threshold price
14 that CV Therapeutics determined and stated in the draw-down notice. The threshold price set could
15 not be below \$20 per share without Acqua Wellington's consent.

16 52. Pursuant to this agreement, CV Therapeutics exercised its rights and forced the sale
17 of stock to Acqua Wellington during the Class Period. On January 29, 2003, defendants sold
18 378,089 shares of common stock to Acqua Wellington, for net proceeds of \$6,943,778. These shares
19 were priced from January 21-27, 2003. Again, on March 24, 2003, pursuant to this agreement,
20 defendants forced Acqua Wellington to purchase 700,000 shares of CV Therapeutics common stock,
21 for net proceeds of \$11,828,000. These shares were priced from March 17-21, 2003. Applicable
22 NASDAQ national market rules, however, limit the number of shares that CV Therapeutics may
23 issue under the agreement with Acqua Wellington. As of April 4, 2003, the parties had reached their
24 limit, therefore, on April 4, 2003, CV Therapeutics and Acqua Wellington mutually agreed to
25 terminate the agreement in accordance with its terms.

26 53. Thereafter, on July 3, 2003, CV Therapeutics and Acqua Wellington executed
27 another, similar "equity line of credit" agreement. In accordance therewith, on September 16, 2003,
28 CV Therapeutics forced Acqua Wellington to sell 587,489 shares of stock for net proceeds of

1 \$14,960,000. These shares were priced from September 8-12, 2003. The higher the stock price, the
2 more money defendants gained per share of stock. This agreement allowed defendants to obtain
3 more money, while selling less stock to Acqua Wellington.

4 54. Defendants were further motivated to commit fraud in order to obtain more cash
5 through the issuance of securities. On June 12, 2003, defendants announced the sale of \$100 million
6 aggregate principal amount of its 2.00% senior subordinated convertible debentures through a
7 private placement. This transaction closed June 18, 2003.

8 55. Defendants attempted, yet again, to obtain further financing while the Company's
9 securities remained inflated. On October 3, 2003, defendants filed a mixed-shelf registration
10 statement for \$300 million in debt securities. To date, however, the Company has not issued any
11 securities under this October 3, 2003 registration statement. Given the negative October 30, 2003
12 Approvable Letter, the facts revealed before and during the December 9, 2003 Advisory Committee
13 meetings and the subsequent series of stock drops, it is unlikely that defendants will issue any
14 securities under this registration statement in the near future.

15 56. Through these various financings, CV Therapeutics wound up with over \$400 million
16 in cash. When questioned by an analyst on October 17, 2003, as to why CV Therapeutics needed so
17 much now, Lange responded merely "The philosophy of CV Therapeutics has been to keep a strong
18 balance sheet," to which the analyst responded, "I'm kind of suspicious." Ex. 17 (Conf. Call, Oct.
19 17, 2003).

20 57. Defendants were also motivated to hide the true facts about Ranexa in order to
21 preserve their salaries, bonuses and other compensation, and to allow them to sell stock at inflated
22 prices. If the truth came out about CV Therapeutics, defendants' compensation and the value of
23 their stock would have been jeopardized.

24 **B. Knowledge/Deliberate Recklessness**

25 58. Each Individual Defendant had knowledge of CV Therapeutics' problems and was
26 motivated to conceal such problems. Each worked closely with the others and was in a position to
27 know key information. Ex. 18 (organizational chart). Spiegelman, as CFO, was responsible for
28 financial reporting and communications with the market. Defendant Lange, as CEO and Chairman,

1 was responsible for press releases issued by the Company. Speigelman and Lange signed the
2 documents filed with the SEC. Belardinelli, as Vice President of Drug Research and
3 Pharmacological sciences, was responsible for clinical development. As revealed by the confidential
4 witnesses, defendants Lange and Belardinelli attended the meetings where Ranexa's QT
5 prolongation problems were discussed. Each Individual Defendant sought to demonstrate that he
6 could lead the Company successfully and generate the growth expected by the market.

7 59. Defendants recognized the importance of being brutally honest with the investment
8 community surrounding issues of QT prolongation. In an April 22, 2002 conference call with
9 securities analysts, given by the Lange and Speigelman, Lange stated:

10 I just went to talk a little about QTC [sic]. Obviously, it is a very topical
11 issue.... You are going to begin to read more about it with respect to ranolazine, and I
12 really do think it will become more and more important in how regulatory agencies
including especially the FDA view compounds that have modest small impact on
QTC [sic].

13 * * *

14 I think it is fair for investigators, *investors*, and FDA to be asking what could it
15 mean

16 Ex. 19 at 2, 9 (Conf. Call. Apr. 22, 2003).

17 60. Three confidential witnesses have come forward, revealing that upper management
18 were extremely concerned about the QT prolongation issues and spent a great deal of time
19 messaging the results of the Company's studies on QT interval prolongation in order to minimize
20 the frequency and magnitude of the prolongation below the FDA's guidelines. These witnesses
21 corroborate one another and were in positions of authority, such that their information is both first-
22 hand and reliable. See Ex. 1 (witness interviews appended to this Complaint).

23 **CORE UNDISCLOSED MATERIAL ADVERSE FACTS**
24 **DURING THE CLASS PERIOD**

25 61. While CV Therapeutics and the Individual Defendants were publicly expressing
26 satisfaction with the progress Ranexa was making with the FDA toward approval, behind the scenes
27 another, far less favorable, story was taking place.
28

1 **A. Defendants' Significant Concerns About QT Data**

2 62. CV Therapeutics was seriously concerned that the QT data on Ranexa was so out of
3 line with FDA guidance that Ranexa would not get approved.

4 (a) In a monthly meeting of his staff in November/December 2002, Dr. Andrew
5 Wolff, Senior Vice President of Clinical Research and Development, and who was one of defendant
6 Lange's direct reports responded to a presentation by Marcus Jerling, Vice President of Clinical
7 Research, on QT prolongation studies and research, saying, "Oh boy, we need to work on this!"
8 Wolff then asked Jerling what he was doing to address this issue. Jerling responded that he was
9 looking at different techniques to calculate QT prolongation. CW1². Jerling told another CV
10 Therapeutics employee to apply techniques on another drug, some of which were applied on Ranexa
11 for the Summary Basis of Approval. These techniques, however, were not all accepted by the FDA,
12 and show the desperate nature of defendants' concern about the QT/QTc prolongation data on
13 Ranexa. CW1 and CW2.

14 (b) In the fall of 2002, Jerling and defendant Belardinelli, who reported directly to
15 defendant Blackburn, attended a Drug Information Association meeting which discussed the clinical
16 relevance of QT prolongation and the FDA's guidance. Upon return, Belardinelli told CW1, in
17 reference to the QT prolongation problems with Ranexa, "I don't think it looks good for us."

18 63. The data from the clinical studies of Ranexa showed that QT interval prolongation
19 caused by Ranexa exceeded the 20 msec prolongation/500 msec interval guideline established by the
20 FDA. There were at least 10 to 15 instances of patients with QT intervals above 500 msec and
21 several instances of prolongation over 20 msec. CW1. Defendants, therefore, manipulated the
22 analysis of the data to decrease both the magnitude and frequency of QT prolongation below the
23 level that would cause the FDA concern. CW1, CW2, CW3. In order to accomplish this, the
24 statisticians were asked to apply "correction formulas" and alternate the value of several variables,
25 including gender, age, ventricle index and diabetes factors. CW2.

26
27 ² "CW" refers herein to the confidential witnesses as described in Ex. 1 appended hereto. CWs
28 are differentiated numerically (*i.e.*, CW1, CW2, etc.).

1 64. According to the Cardiovascular and Renal Drugs Advisory Committee, “Briefing
2 Document, Ranexa™ (ranolazine) Extended Release Tablets NDA 21-526,” prepared by CV
3 Therapeutics, (“Briefing Document”), and released for public disclosure without redaction on or
4 about December 9, 2003:

5 (a) The average increase associated with the maximum dosage (1000 mg) was
6 approximately **20 msec** (Ex. 20 at 125 Briefing Document);

7 (b) There were 46 increases of = 60 msec for uncorrected change in QT (*id.* at
8 126-27);

9 (c) Using a corrected change of QT or QTc there were dozens of QT prolongation
10 over 20 msec (*id.* at 130);

11 (d) Though uncorrected QT is now shown, there were 53 patients with QTc over
12 500 msec using the Bazett correction, and 20 using the Fridericia corrections formula (*id.* at 140);
13 and

14 (e) Two patients who reported QTc values > 500 msec died suddenly. Ex. 21 at 6
15 (FDA’s Division of Cardio-Renal Drug Products, Secondary Review, Sept. 29, 2003 (“Secondary
16 Review”)).

17 65. Defendants were so concerned about the possibility that the QT/QTc prolongation
18 would cause Ranexa to be rejected for use to the general population that unbeknownst to the public,
19 defendants sought to gain its approval only as a second-line therapy. This was disclosed in their
20 proposed dosing labeling. Defendants’ proposed labeling submitted to the FDA stated that the
21 proposed indication was for “treatment of chronic angina patients with severe coronary artery
22 disease, ***and should be reserved*** for use in patients in whom other anti-anginals are inadequate or not
23 tolerated.” Ex. 25 at 2 (Integrated Summary of Efficacy.)

24 66. Defendants, however, repeatedly misrepresented to the public that the QT
25 prolongation experienced was not of any concern. They further misleadingly represented that the
26 data was below the FDA’s guidelines of “concern,” with no instances of prolongation over 20 msec
27 and only three patients with intervals over 500 msec. Ultimately, the FDA performed a “reverse
28 analysis” of the data and determined that the QT numbers did not add up. As a result, the FDA

1 requested that CV Therapeutics perform an “interim analysis” and declined to review Ranexa in
2 September 2003. CW3. In its Approvable Letter, the FDA determined that defendants must conduct
3 additional clinical studies to address the FDA’s questions concerning QT prolongation.

4 **B. The FDA’s Undisclosed Concerns Regarding Ranexa’s Propensity to Cause QT**
5 **Prolongation and Issuance of a Discipline Review Letter**

6 67. Simultaneous with defendants’ statements that the Ranexa-induced QT prolongation
7 was a mere “perception of a risk,” the FDA was documenting serious concerns with the safety and
8 efficacy of the drug. The Clinical Review prepared by the FDA and released to the public on
9 December 8, 2003, reveals that the FDA met four times with CV Therapeutics before the filing of
10 the NDA – July 25, 2000, December 20, 2001, August 13, 2002 and October 10, 2002. Ex. 4 at 13
11 (Clinical Review). Concerns raised during the July 2000 meeting include QT prolongation as a
12 “major concern” such that additional safety data was needed. *Id.*

13 68. On October 10, 2002, the FDA stated, in order for the drug to be approved for use in
14 resistant populations it must be shown that maximal doses of beta blockers and calcium channel
15 blockers have been used, and that additional safety data would be needed to show that ranolazine
16 was not inherently harmful to intolerant subgroups who are clearly intolerant to conventional
17 therapy.

18 69. Because of QT concerns, at several points in the development of Ranexa, the FDA
19 encouraged CV Therapeutics to study the use of Ranexa in a population with refractory angina. In a
20 letter to the FDA’s Dr. Throckmorton, dated September 29, 2003, CV Therapeutics finally agreed:

21 “It therefore appears reasonable to allow a trial of ranolazine in those patients in
22 whom the currently available agents have been demonstrated to be either inadequate
23 or not tolerated. For those among them whose angina symptoms are decreased by
24 ranolazine, the benefit will surely justify the risk of any of the small QT effect.”

25 Ex. 21 at 8 (Secondary Review).

26 70. Sometime subsequent to the acceptance of filing of the NDA in March 2003, but prior
27 to September 13, 2003, the FDA sent to CV Therapeutics a discipline review letter (“DR letter”)
28 outlining deficiencies found by various discipline review teams for their portions of the pending
NDA for Ranexa. These deficiencies were so serious that CV Therapeutics submitted an
amendment to the NDA, dated September 13, 2003 (and received by the FDA on September 15,
CONSOLIDATED COMPLAINT FOR VIOLATION OF THE FEDERAL
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1 2003). The amendment provided non-clinical study reports to address pharmacology/toxicology
2 issues discussed in the letter. Among other things, CV Therapeutics attempted to prove that QT
3 Prolongation with ranolazine was not a concern. Ex. 22 (Memorandum Regarding Nonclinical
4 Electrophysiological and Proarrhythmic Effects of Ranolazine from John Koerner, Ph.D. to
5 Douglas Throckmorton, dated October 23, 2003).

6 **C. The FDA Had Notified CV Therapeutics that Its QT Prolongation Data Was**
7 **Inadequate**

8 71. According to the approach mandated by the FDA Cardiovascular and Renal Drug
9 Products Advisory Committee on November 15, 2002 and in accordance with the FDA's guidance
10 paper (Ex. 15), the FDA stated that in assessing the safety of drugs which cause QT interval
11 prolongation, the Agency would review pre-clinical data. In the case of a cardiac drug, this
12 necessarily would include analysis of ECG data. Yet, according to FDA internal notes, defendants
13 failed to provide ECG data from dog and preclinical studies, despite this guidance and repeated
14 requests. *On May 16, 2003, the FDA contacted CV Therapeutics* to request the ECG data on the
15 dog studies, since none had been presented. Ex. 23 at 68-70 (Pharmacology/Toxicology Report).
16 According to Dr. Elizabeth A. Hausner of the FDA's Division of Cardio-Renal Products, "[t]he
17 sponsor was asked by telephone to provide [the pre-clinical studies] ECG data" since no ECG data
18 was provided. "[*On*] July 2, 2003 the sponsor replied verbally to this request and said that the ECG
19 data was unavailable and *could not be produced.*" *Id.* at ii and iii. Again, on July 31, 2003, a further
20 conference was held over the lack of pre-clinical data:

21 "In a July 31, 2003 telecon with representatives from CV Therapeutics, Drs
22 Koerner and Hausner requested the ECG data for the dog toxicology studies. August
23 18, 2003, in a telephone call, Margaret Dillon of CV Therapeutics informed this
24 [FDA] reviewer that *while the ECG data had been located, it had not been*
analyzed. She estimated that it would take some 6 months of work to quantitate the
various ECG intervals. After consultation with Drs Koerner and Gordon, it was
decided to forgo review of the dog ECG data. This was communicated back to the
sponsor later on 8/18/03."

25 *Id.*

26 72. Despite Drs. Koerner's and Gordon's decision to forego review of the ECG data for
27 dog toxicology studies, defendants filed an amendment to the NDA on September 13, 2003
28

1 analyzing this data, among other things. Ex. 22 (Koerner Memo. to Throckmorton, dated Oct. 23,
2 2003). Dr. Throckmorton ultimately concluded that *“much of the animal work was done using a
3 lower standard of quality than is now in place,” such that while, “no clear signal of concern
4 regarding changes in the QT interval can be found in the standard cardiac evaluations of the
5 animals ... methodological flaws prevent this from being reassuring.”* Ex. 24 at 2-4 (Divisional
6 Memorandum, Oct. 28, 2003).

7 **D. Other Undisclosed Problems with the Ranexa Studies**

8 73. QT prolongation was not the only significant problem with the Ranexa studies.

9 (a) The studies conducted by CV Therapeutics revealed that Ranexa is
10 significantly less effective in women, only 22% of those enrolled in the clinical studies were women.
11 Ex. 4 at 16, 21-22 (Clinical Review); Ex. 25 at 2 (Integrated Summary of Efficacy).

12 (b) Incredibly, 98% of the study population was Caucasian, such that the FDA
13 was unconvinced that safety in other race groups had been established. Ex. 4 at 22 (Clinical
14 Review); Ex. 25 at 2 (Integrated Summary of Efficacy).

15 (c) While defendants sought approval of the sustained-release formulation, the
16 majority of their studies only used the immediate release formulation. Ex. 25 at 2 (Integrated
17 Summary of Efficacy).

18 (d) The Ranexa studies' size failed to conform with the ICH Harmonised
19 Tripartite Guideline, the Extent of Population Exposure to Assess Clinical Safety (ICH E1) which,
20 according to the FDA Committee Questions dated December 9, 2003 recommends a use of at least
21 1,500 individuals treated with relevant doses. According to the FDA, only 1,359 were treated with
22 500 bid or more, and only 852 for more than 30 days. Substantially less than were tested for 750
23 bid. Only 825 were treated with 1000 bid or more, and only 536 for more than 30 days. Ex. 26
24 (Committee Questions).

25 (e) The trials in angina did not adequately characterize the relationship between
26 dose and therapeutic effect to provide labeling instruction for its use. Ex. 3 (Approvable Letter, Oct.
27 30, 2003).

28

1 (f) Great inter-subject variability in these plasma levels and the small number of
2 studies exploring the dose range of ranolazine in patients with angina made it difficult to adequately
3 describe in labeling how ranolazine should be dosed. *Id.*

4 (g) In the August 2002 pre-NDA meeting, the FDA noted that “in CVT 3033,
5 patients did not receive an adequate dose of amlodipine, atenolol and diltiazem and therefore
6 interpretation of ranolazine’s effect as add-on therapy was difficult.” In addition, “a consumption
7 was seen in (only) one study (CVT3033).” Therefore, the FDA concluded, “[r]esults of the clinical
8 **studies do not support the proposed labeling**, which gives a starting dose of 500 mg bid with
9 upward titration through 750 mg bid to 1000 mg bid, as needed, based on clinical response.” Ex. 4
10 at 10, 13 (Clinical Review).

11 (h) Unresolved efficacy issues included: 1) efficacy of ranolazine when added to
12 maximal doses of anti-anginal(s); 2) comparisons to other anti-anginals; 3) efficacy in a refractory
13 population; and 4) Complete exploration of dose-response relationship such that efficacy at lower
14 doses are identified. *Id.* at 7.

15 (i) The study population in studies 3033 and 3031 was over 90% Caucasian.
16 Therefore, there were insufficient numbers of non-Caucasians to provide a meaningful analysis of
17 racial/ethnic differences. *Id.* at 10.

18 (j) The available data was inadequate to determine whether there was evidence of
19 testicular toxicity by ranolazine. Ex. 3 (Approvable Letter, Oct. 30, 2003).

20 (k) An effect on the QT interval was seen in all patient populations studied and
21 CV Therapeutics had **neither provided sufficient rationale for discounting this as a potential**
22 **clinical concern** nor devised dosing strategies that would avoid significant QT prolongation in some
23 patients. *Id.*

24 (l) **[G]iven the availability of other anti-anginal drugs that do not prolong the**
25 **QT interval, there needs to be a clear reason to approve a therapy with what appears to be an**
26 **additional, possibly life-threatening risk.** Ex. 4 (Clinical Review).

1 (m) The database had information on fewer than 1000 patients given relevant
2 doses of ranolazine for at least one month, an exposure well below what is typically expected for
3 chronic treatment for a symptomatic claim. Ex. 3 (Approvable Letter, Oct. 30, 2003).

4 **E. The Misleading Premature Announcement of a September 15, 2003 Date for Review by
5 the Advisory Committee**

6 74. Defendants falsely and/or misleadingly announced that a September 15, 2003
7 Advisory Committee Review Meeting had been “noticed” and “scheduled” when none in fact had
8 been actually “noticed” or “scheduled.”

9 75. Public noticing requirements for an FDA advisory committee meeting are given by 21
10 CFR §14.20, entitled, “Notice of hearing before an advisory committee.” The regulation states:

11 Sec. 14.20 Notice of hearing before an advisory committee.

12 (a) *Before the first of each month, and at least 15 days in advance of a*
13 *meeting*, the Commissioner *will publish a notice* in the Federal Register of all
14 advisory committee meetings to be held during the month. Any advisory committee
15 meetings for that month called after the publication of the general monthly notice are
16 to be announced in the Federal Register on an individual basis at least 15 days in
17 advance. The Commissioner may authorize an exception to these notice requirements
18 in an emergency or for other reasons requiring an immediate meeting of an advisory
19 committee, in which case public notice will be given at the earliest time and in the
20 most accessible form feasible including, whenever possible, publication in the
21 Federal Register.

22 76. The FDA establishes and maintains tentative dates and general information for
23 advisory committee meetings on its website and through its advisory committee telephone
24 information line. A continually updated month by month calendar of tentative and confirmed
25 advisory committee meeting dates can be accessed at
26 <http://www.fda.gov/oc/advisory/accalendar/accalendar.html> (“calendar webpage”). Dates indicated
27 on this calendar are tentative and will not be confirmed until FDA causes a public notice to be
28 published in the Federal Register.

77. A telephone hotline that provides information regarding tentative and confirmed
meetings of FDA advisory committees is described at
<http://www.fda.gov/ohrms/dockets/ac/listinfo.htm>. While the hotline is a convenient method to
disseminate tentative information about the advisory committee calendar, it cannot be used to signal

1 the intent of the FDA to go forward with any particular meeting, since the FDA will not officially
2 announce a schedule for a meeting to the public until it causes a notice to be published in the Federal
3 Register.

4 78. Once the FDA makes the decision to publish a notice in the Federal Register to go
5 ahead with a hearing for applicants and interested parties on matters before an advisory committee,
6 the FDA *will update the calendar webpage* to include a link to a new webpage containing the
7 schedule and details for the meeting, plus a link to the Federal Register notice. If the meeting is
8 updated, postponed or cancelled, *the words “updated,” “postponed” or “meeting cancelled!”* are
9 indicated in red on the webpage, with explanatory remarks.

10 79. For a September 15-16, 2003 meeting to have been formally scheduled and cancelled
11 by FDA, a webpage announcing the meeting, with “meeting cancelled!” indicated in red would
12 appear. In fact, there are no links, indications of a tentative September 15-16, 2003 meeting date or
13 change in schedule on the “calendar webpage.”

14 80. In preparation for an advisory committee meeting, by regulation, both the FDA and
15 the applicant company must provide their respective “white papers,” analyzing the drug, to the
16 advisory committee 30 days prior to the scheduled meeting. A September 15, 2003 Advisory
17 Committee meeting, therefore, would have triggered an August 15, 2003 deadline for submission of
18 CV Therapeutics’ and the FDA’s materials. Ex. 27 at 3 (Mid-Quarter Conference Call, Aug. 4,
19 2003).

20 81. A September 15, 2003 Advisory Committee meeting would have further triggered a
21 July 15, 2003 Federal Registry queue date. *Id.* The failure for notice to appear in the registry means
22 that the FDA has not scheduled an advisory committee meeting.

23 82. According to 21 C.F.R. §14.20, the FDA must publish notice in the Federal Register
24 of an upcoming Advisory Committee meeting. According to defendant Lange, a September 15,
25 2003 Advisory Committee meeting required “a 7/15 federal registry queue date.” *Id.* Yet, notice for
26 a September 2003 meeting was never published in the Federal Register.

1 83. Moreover, defendant Lange, in the August 4, 2003 conference call, admits to having
2 prematurely announced the Advisory Committee meeting before it was published in the Federal
3 Register, having jumped the gun and to not being ready:

4 ERIC SCHMIDT:

5 Maybe you could speculate as to why they called for the September panel to begin
6 with?

7 LOUIS LANGE:

8 You know, it really is driven by the timelines ... you know, in some ways a place
holder events.

9 * * *

10 STUART WISENARD:

11 Good morning, guys. Two questions: First, the panel was never in the pink sheets, I
12 don't think it was in the "Federal Register." Do you think you were jumping the gun
by announcing it before you were really ready to go to the panel? ...

13 LOUIS LANGE:

14 No, a good question, Stu. We certainly thought about that at the time and
15 even in retrospect and, you know, obviously, today we wish we hadn't done it, but I
16 want to say we were told by the FDA that we were going to a September panel. And,
17 you know, that was in the queue for the federal registry. It would have hit that,
probably today, August 4, and in order to really pull it, you know, we sort of had the
last opportunity to talk to them on Friday.

18 So it was going to come out ... [t]o wait until we have it in triplicate, signed
and stamped by everybody, for a big, material event is not in anybody's interest...."

19 Ex. 27 at 9-10 (Conf. Call, Aug. 4, 2003).

20 84. In fact, as discussed in ¶¶71-72 above, at the time CV Therapeutics announced the
21 September 2003 Advisory Committee meeting, the FDA was still awaiting ECG data from the pre-
22 clinical and dog studies requested earlier. CV Therapeutics likely received a discipline letter and
23 had decided to amend the NDA. Defendants, therefore, knew or were at least deliberately reckless in
24 announcing a September 2003 review meeting.

25 **F. The Undisclosed Portions of the FDA "Approvable Letter" Announced October 30,
26 2003**

27 85. On October 30, 2003, the FDA issued an Approvable Letter with conditions,
28 requesting additional clinical information. The Company disclosed only that the FDA "indicated

1 that there is evidence that Ranexa is an effective anti-anginal, and that additional clinical information
2 is needed prior to approval. We understand that the FDA may be prepared to reevaluate this
3 requirement based on the results of the Advisory Committee review.” Ex. 28 (Press Release, Oct. 30
4 2003). In fact, the Approval Letter was far less favorable. Rather, it stated:

5 Approval is contingent on your adequately addressing the deficiencies listed below.
6 Because **substantial additional clinical data are needed**, no labeling will be included
7 with this letter.

8 Based on our reviews of the submitted materials, there is evidence that
9 ranolazine is an effective anti-anginal drug in an **undifferentiated** population of
10 patients, including patients receiving sub-maximal treatment with other anti-anginals.
11 **The trials in angina, however, do not adequately characterize the relationship**
12 **between dose and therapeutic effect sufficiently to provide labeling instructions for**
13 **its use.** Our analyses suggest a relationship of ranolazine concentrations in plasma to
14 clinical effects. However, the great inter-subject variability in these plasma levels
15 and **the small number of studies exploring the dose range of ranolazine in patients**
16 **with angina** make it difficult to adequately describe in labeling how ranolazine
17 should be dosed. In study CVT 3033, for instance, doses of 750 mg and 1000 mg
18 were not distinguishable from each other in their effects on exercise tolerance. In
19 study CVT 3031, a crossover design and short treatment period (just one week) were
20 used, and the results suggest that doses of 1000-1500 mg b.i.d. were more effective
21 than a dose of 500 mg BID. **It will be necessary to obtain additional dose-response**
22 **information.** In addition, the Agency has **three important safety concerns that will**
23 **need to be addressed** prior to approval:

24 1) Potential testicular toxicity, manifest as impaired fertility in rats in
25 study AT-4136116-R-86-43285-PO-RMF. The **available data are inadequate** to
26 determine whether this was a chance finding or evidence of testicular toxicity by
27 ranolazine. While no clinical signs of male reproductive toxicity were reported, this
28 is not surprising or reassuring, as adequate assessment of this toxicity typically
requires targeted clinical evaluation.

1) Delayed cardiac repolarization, manifest clinically as prolongation of
the QT interval. An effect on the QT interval was seen in all patient populations
studied, particularly at higher blood concentrations of ranolazine, and **you have**
neither provided sufficient rationale for discounting this as a potential clinical
concern nor devised dosing strategies that would avoid significant QT prolongation
in some patients. In particular, in certain populations (e.g., patients with hepatic
impairment and those taking inhibitors of CYP3A4 or the P-glycoprotein
transporter), larger effects of ranolazine on the QT interval were seen or can be
expected. **Given that you have demonstrated effects on a symptom (i.e., angina),**
and given the availability of other anti-anginal drugs that do not prolong the QT
interval, there needs to be a clear reason to approve a therapy with what appears to
be an additional, possibly life-threatening risk.

3) Adequate safety exposure. The present database has information on
fewer than 1000 patients given relevant doses of ranolazine for at least one month,
an exposure well below what is typically expected for a chronic treatment for a
symptomatic claim.

1 To resolve the issue of potential testicular toxicity, *additional animal data*
 2 *are needed*, beginning with a more thorough review of the available histologic
 3 materials from the chronic animal toxicity studies. Depending on the outcome of that
 4 review, *additional animal studies may be needed*. Should a toxic effect of
 ranolazine on the testes be confirmed, the clinical consequences of this toxicity will
 need to be understood.

5 ***Regarding the effects of ranolazine on cardiac repolarization, we are not***
 6 ***convinced by the available data that the effects of ranolazine on the QT interval***
 7 ***would not lead to increased risk of arrhythmias at doses and in populations where***
 8 ***it is likely to be used***. To address this concern, you could provide data demonstrating
 9 that ranolazine has benefits that offset the concern arising from the effects on the QT
 10 interval. In patients with angina, this additional benefit could include showing
 11 efficacy in populations not adequately treated with maximally-tolerated or labeled
 12 doses of more than one class of approved anti-anginals. Such data should be
 13 obtained from randomized, prospectively-designed trials, exploring a broad range of
 14 doses of ranolazine, to be conducted following discussions with the Agency.
 15 Demonstration of a benefit on fixed clinical endpoints, such as myocardial infarction
 16 or death, also would obviously overcome concerns about effects on the QT interval.
 17 ***The available data suggest a smaller effect of ranolazine in women with angina;***
 18 ***future clinical studies should further characterize this apparent gender difference.***
 19 Finally, such a trial could satisfy the need for a larger safety database.

20 * * *

21 ***Within 10 days after the date of this letter, you are required to amend this***
 22 ***application, notify us of your intent to file an amendment, or follow one of your***
 23 ***other options under 21 CFR 314.110***. If you do not follow one of these options, we
 24 will consider your lack of response a request to withdraw the application under 21
 25 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will
 26 not process a partial reply as a major amendment ***nor will the review clock be***
 27 ***reactivated until all deficiencies have been addressed***.

28 Under 21 CFR 314.102(d), you may request an informal meeting or telephone
 conference with the Division of Cardio-Renal Drug Products to discuss what steps
 need to be taken before the application may be approved.

Ex. 3 (Approvable Letter).

G. CV Therapeutics' Efficacy Data Was Insufficient

86. Defendants continuously represented that Ranexa did, in fact, effectively treat chronic
 angina. As of the time of the announcement of the alleged September Advisory Committee meeting,
 however, the data showed that Ranexa simply "would never work." CW4. Moreover, the FDA
 Director of the Division of Cardio-Renal Products, Throckmorton, concluded that "*the available*
efficacy data [on Ranexa] are modest at best." Ex. 3 (Approval Letter).

1
2 **DEFENDANTS' FALSE AND MISLEADING STATEMENTS**
3 **ISSUED DURING THE CLASS PERIOD**

4 **False and/or Misleading Statement**

5 87. Defendants' fraudulent scheme commenced on December 30, 2002, upon the filing of
6 the NDA with the FDA. On December 30, 2002, CV Therapeutics issued a press release (listing
7 Speigelman as the contact and quoting Lange) announcing the filing of the Ranexa NDA. In
8 relevant part, the press release states:

9 CV Therapeutics, Inc. (Nasdaq: CVTX) announced today that *it has submitted a new*
10 *drug application* (NDA) for Ranexa(TM) (ranolazine) to the U.S. Food and Drug
11 Administration (FDA) seeking approval of Ranexa for the treatment of chronic
12 angina. *If approved*, Ranexa, which partially inhibits fatty acid oxidation (pFOX),
13 *would represent the first* in a new class of anti-anginal therapy in more than 20
14 years.

15 *"This NDA submission is important* because Ranexa could offer a potential
16 new approach to the treatment of chronic angina. We believe that Ranexa could
17 address the need for new treatment options for angina," said Louis G. Lange, M.D.
18 Ph.D., chairman and chief executive officer of CV Therapeutics.

19 The NDA consists of more than 300,000 pages in over 1,100 volumes, and contains
20 data from more than 3,300 angina patients and healthy volunteers, including over
21 25,000 electrocardiograms.

22 Chronic angina is a serious and potentially debilitating heart condition,
23 usually associated with coronary artery disease and marked by repeated and
24 sometimes unpredictable attacks of chest pain. The condition can significantly
25 compromise patients' lives, causing many patients to curtail activities to avoid an
26 attack.

27 Chronic angina is a growing health problem, affecting millions of people,
28 generally over the age of 55. Annually, it costs the nation tens of billions of dollars
in healthcare services and lost work. Approximately 6.4 million people in the U.S.
live with chronic angina, with an additional 400,000 people newly diagnosed each
year. The U.S. Census Bureau projects that the 55-plus age group – the group most
at-risk for angina – will increase by 80 percent over the next 30 years.

CV Therapeutics is a development-stage company. None of its products have
been approved for marketing by the United States Food and Drug Administration
(FDA) or other foreign regulatory agencies. Any products of the company discussed
here are currently under investigation in clinical trials subject to United States
Investigational New Drug (IND), and as applicable, appropriate clinical trial
applications to regulatory authorities outside the United States. CV Therapeutics'
products have not been determined to be safe or effective in humans for any uses.

Ex. 29, (Press Release, Dec. 30, 2002).

1 88. Also on December 30, 2002, CNBC interviewed defendant and CEO Lange, asking
 2 specifically about the QT prolongation effect. In response, defendant Lange made the first of a
 3 series of false and misleading statements downplaying to the public the existence and significance of
 4 the QT interval prolongation observed in the clinical studies of Ranexa:

5 *CNBC/Dow Jones - Business Video, December 30, 2002, Monday*

6 KERNEN: Good to see you. In looking over some of the comments from the
 7 analysts, I don't even know what this is, maybe you can explain it to me. But
 8 something called "**QTC prolongation**" is what one individual analyst is worried
 9 about when you go before, presumably, if you were to go before a panel at end of
 10 next year, they view this as a high-risk application because of that. What is that? a
 11 side effect to this new class of chronic angina drugs?

12 LANGE: Good question. Joe, I used to be chief of cardiology at one of the
 13 teaching hospitals in the Midwest. **And a QT effect can appear in cardiograms.**
 14 And with some drugs it's bad. A lot of drugs are on the market, and it's not so bad.
 15 ***We believe that for Ranolazine (ph) it won't be a particular problem for ultimate***
 16 ***review by the agency. It will be discussion item.*** And we think Ranolazine is the first
 17 in a new class of drugs that works by maintaining heart rate blood pressure....”

18 Ex. 30 (CNBC/Dow Jones Interview, Dec. 30, 2002).

19 89. In follow-up conversations with analysts, defendants repeated their false and
 20 misleading statements pertaining to the QT interval prolongation data. Mark Monane, M.D. of
 21 Needham & Company, Inc. (“Needham”) issued an analyst report on February 6, 2003 which was
 22 based on and repeated information provided by management, stating:

23 After meeting with management yesterday, we feel even more confident
 24 regarding the Ranexa NDA as well as the increasing amount of evidence supporting
 25 the benefit/risk ratio of Ranexa. ***The corporate presentation now highlights new***
 26 ***data which supports Ranexa for the treatment*** [of] patients suffering from chronic
 27 angina. These new data points include:

28 * * *

- analysis of outliers demonstrating no single patient with a consistent large
 increase in QTc (3 MARISA patients with QTc measurements over 500msec – 2
 were on Ranexa and 1 placebo; 2 CARISA patients with QTc measurements over
 500msec – 1 was on Ranexa and 1 placebo)

Ex. 31 (Needham Report, Fed. 6, 2003).

90. On March 5, 2003, CV Therapeutics issued a press release, giving defendant
 Speigelman as the contact person, further highlighting the “mechanical” progress of Ranexa through
 the FDA’s approval process. The press release announced that the FDA accepted the Company’s

1 NDA for Ranexa for filing, and stated: “Based on this *acceptance*, the FDA will review the NDA. *If*
 2 *approved, Ranexa ... would represent the first in a new class of anti-anginal therapy in more than*
 3 *20 years.*” Ex. 32 (Press Release, Mar. 5, 2003).

4 91. On March 18, 2003, CV Therapeutics and Speigelman issued another press release on
 5 Ranexa. This press release announced the receipt of a Notice of Allowance of two newly-issued
 6 patents on Ranexa significantly broadening the claims to include use for additional cardiovascular
 7 uses including treatment of arrhythmias. Ex. 33 (Press Release, Mar. 18, 2003).

8 **Reasons False and/or Misleading**

9 92. Defendants’ statements on December 30, 2002, the follow-up conversations with
 10 analysts and the March 5 and 17, 2003 press releases were false and/or misleading at the time they
 11 were made, as explained in “Defendants’ Significant Concerns About QT Data,” ¶¶62-66;
 12 “Defendants Failed to Disclose the FDA’s Concerns Conveyed to Defendants, the Discipline Review
 13 Letter and the NDA Amendment,” ¶¶67-70; “Defendants Hid Other Material Deficiencies in the
 14 NDA,” ¶73; “The Efficacy Data was Deficient.” ¶86.

15 **False and/or Misleading Statement**

16 93. Defendants continued to downplay to the public the existence and significance of the
 17 QT interval prolongation observed in the clinical studies of Ranexa. On February 19, 2003, the
 18 Company held its 4Q02 Financial Release Conference Call. During the call, defendant Lange stated:

19 *“We believe that the risk is really a perception of a risk, and that is because of the*
 20 *small mean QTC [sic] effect, as we recently have been describing across our*
 21 *database. At the peak drug concentration in the coriticol [sic] [clinical] range, it is*
a very small effect, 2-5milliseconds smaller in fact, than in other drugs that were
approved recently.”

22 Ex. 34 (Conf. Call, Fed. 19, 2003).

23 94. On April 16, 2003, defendants Lange and Speigelman held a conference call with
 24 analysts. In that conference call, Lange stated:

- 25 • “The first quarter of ’03 was a busy one for CVT [CV Therapeutics], highlighted by the
 26 acceptance for review of our Ranexa NDA by the FDA.”
- 27 • The NDA was a “very comprehensive package representing data from over 3300 angina
 28 patients and subjects....”
- “We certainly as a company believe that the benefit is significant....”

- “The QTc increase is fairly small at some order in the clinical range of 2-5 milliseconds at peak blood concentration....”

Ex. 35 (Conf. Call, Apr. 16, 2003).

95. In follow-up calls with analysts, defendants repeated their false statements on the QT interval prolongation data results:

(a) On April 17, 2003, Akhtar Samad, M.D., Ph.D. of Bear Stearns issued an analyst report which was based on and repeated information provided by management, stating:

Recently, CV Therapeutics released additional data on Ranexa. Specifically, *the Company indicated that only 3 patients (2 on Ranexa and 1 on placebo) in the MARISA study had a QTc measurement of over 500msec and more importantly none of these patients stayed above 500msec through subsequent ECG readings or had serious arrhythmias. With respect to CARISA, management indicated that only 2 patients (1 on Ranexa and 1 on placebo) had a QTc measurement above 500msec ... through subsequent ECG measurements or had serious arrhythmias.*

Ex. 36 (Bears Sterns, Apr. 17, 2003).

(b) On April 17, 2003, David Webber of First Albany Corp. (“First Albany”) issued an analyst report which was based on and repeated information provided by management, stating:

We continue to believe that the QT prolongation caused by Ranexa is unlikely to delay FDA approval because the effect is small, extreme prolongations are rare and transient, prolongations are no worse in high-risk subgroups, and the benefits of Ranexa appear to outweigh the risks....

Ex. 37 (First Albany, Apr. 17, 2003).

96. On May 15, 2003, CV Therapeutics and defendant Spiegelman issued a press release announcing that “ranolazine attenuated the proarrhythmic effects of ATX-11, a naturally occurring toxin, in three preclinical studies presented at the 24th Annual Scientific Sessions of the North American Society of Pacing and Electrophysiology (NASPE).” Ex. 38 (Press Release, May 15, 2003). Defendant Belardinelli is listed in the press release as one of the authors of the studies.

Reasons False and/or Misleading

97. The statements during the conference call, in follow-up conferences with analysts and in the May 15, 2003 press release were false and/or misleading when made, as set forth in “Defendants Hid Material Concerns About the QT Data,” ¶¶62-66; “Defendants Failed to Disclose the FDA’s Concerns Conveyed to Defendants, the Discipline Review Letter and the NDA

1 Amendment,” ¶¶67-70; “Defendants Hid Other Material Deficiencies in the NDA,” ¶73; “The
2 Efficacy Data Was Deficient.” ¶86.

3 98. On June 13, 2003, the Company issued a press release entitled “CV Therapeutics
4 Announces Private Offering of Senior Subordinated Convertible Debentures.” This transaction
5 closed on June 18, 2003. The press release stated in part:

6 CV Therapeutics, Inc. announced today that it has agreed to sell \$100 million
7 aggregate principal amount of its 2.00% Senior Subordinated Convertible Debentures
8 due 2023 through a private placement to qualified institutional buyers pursuant to
9 Rule 144A and in offshore transactions pursuant to Regulation S under the Securities
10 Act of 1933, as amended. The Company expects to close the transaction on or about
11 June 18, 2003. The Company has also granted to the initial purchasers of the
12 Debentures a 30-day option to purchase up to an additional \$25 million of the
13 Debentures.

14 Ex. 39 (Press Release, June 13, 2002).

15 **False and/or Misleading Statements**

16 99. On July 7, 2003, the Company issued a press release entitled “CV Therapeutics
17 Announces FDA Advisory Committee to Review Ranexa (TM) In September 2003.” The press
18 release stated in part:

19 CV Therapeutics, Inc. announced today that it has been informed by the U.S.
20 Food and Drug Administration (FDA) that the Company’s New Drug Application
21 (NDA) for Ranexa(TM) (ranolazine) for the potential treatment of chronic angina is
22 scheduled for review by the FDA Cardiovascular and Renal Drugs Advisory
23 Committee during its September 15-16, 2003 meeting.

24 Ex. 40 (Press Release, June 7, 2003).

25 100. Defendants repeatedly misrepresented to the investing public that the Advisory
26 Committee was scheduled to review Ranexa on September 15-16, 2003. On July 11, 2003,
27 *Bloomberg* issued a transcript of an interview with defendant Lange entitled “CV Therapeutics’
28 *Lange on Ranexa Outlook, Pipeline.*” The transcript stated in part:

Louis Lange, chief executive of CV Therapeutics Inc., talks with Bloomberg’s
Michael Schneider via satellite from Palo Alto, California, about the biotechnology
company’s product pipeline and Ranexa drug for heart-related problems, which it
may begin selling next year.

SCHNEIDER: We do have, as anticipated, the wrap-up of our series, “Second-
Quarter Stars,” using the Bloomberg terminal to find out companies that have
skyrocketed in share prices in Q2, want to know what’s behind – the driving force
behind the share prices going higher.

1 Well, shares of CV Therapeutics jumped 65 percent in the second quarter.
2 *On Monday, the company said that its application for the heart angina drug,*
3 *Ranexa, I'm going to make sure I got the name pronounced properly in a moment,*
4 *is scheduled for review by the FDA's cardiovascular committee.*

5 Dr. Louis Lange, the chairman and CEO of CV Therapeutics joins us now
6 from Palo Alto, California.

7 Doctor, did I get the name right?

8 LANGE: Yes, sir, Mike. Ranexa would be the first new angina drug in over 20
9 years, and works, importantly, without dropping blood pressure the way the older
10 drugs all do.

11 SCHNEIDER: *Where does it stand in terms of review right now?*

12 LANGE: *Actually, we're really excited about it, because as you said, the notice*
13 *came out Monday that it was going to be at the advisory panel in September, and*
14 *that's after the NDA was submitted about six months ago, the end of last year. So*
15 *we're very excited in mid-September to have a review by FDA. And if that goes*
16 *well, we could actually expect possibly to launch the drug sometime next year.*

17 Ex. 41 (Bloomberg Transcript, July 11, 2003).

18 101. On July 17, 2003, the Company issued a press release entitled "CV Therapeutics
19 Reports 2003 Second Quarter Financial Results." The Company held a conference call with analysts
20 on the same day, July 17, 2003, in which defendants again falsely represented both the QT results of
21 the clinical trials and that Ranexa was to be reviewed by the Cardio Renal advisory committee in
22 September 2003. Specifically, defendant Lange stated:

23 Most importantly, of course, regarding Ranexa, we were invited to the FDA Cardio-
24 Renal Advisory Committee meeting on September 15th, 16th and continue to have a
25 very active and ongoing dialogue with the FDA, and look forward to that meeting in
26 September.

27 * * *

28 THE CALLER: [A]nd what do you see with respect to changes in the EKG on
the QT interval at those higher doses?

DR. LOUIS LANGE: The QT affect that you see there continued to go up, and they
will be in the 10 to 20 millisecond range, but at a very symptomatic level. So, we are
very comforted by the findings in that study."

Ex. 42 (Press Release, July 17, 2003).

Reasons False and/or Misleading

102. These statements on July 7, 2003 and July 11, 2003, announcing and confirming a
September 15-16, 2003 Advisory Committee Review date, were false and/or misleading when made

1 because “Defendants Hid Material Concerns About the QT Data,” ¶¶62-66; “Defendants Failed to
2 Disclose the FDA’s Concerns Conveyed to Defendants, the Discipline Review Letter and the NDA
3 Amendment,” ¶¶67-70; “The FDA Notified Defendants that the QT Data Was Insufficient,” ¶¶71-
4 72; “Defendants Hid Other Material Deficiencies in the NDA,” ¶73; “The Efficacy Data Was
5 Deficient.” ¶86; and:

6 (a) The FDA had not definitively determined whether it would schedule Ranexa
7 for review before the Advisory Committee. In fact, “notice” had not “come out” as Lange stated.
8 *See* ¶¶74-84. Rather, at most, discussions regarding a September review date were preliminary.

9 (b) As of the time of the announcement of this alleged September 2003 Advisory
10 Committee meeting, the FDA had alerted CV Therapeutics of a number of insufficiencies in its data,
11 and requested additional information, for which the FDA was awaiting at the time that CV
12 Therapeutics made its announcement that Ranexa allegedly would be reviewed by the advisory
13 committee. *See* ¶84.

14 (c) Defendants had been on notice at least as of May 16, 2003 that the FDA
15 needed the ECG data from the dog studies during its analysis of the NDA, as alleged in ¶71, and
16 therefore, did not have the pre-clinical or clinical evidence to suggest that Ranexa did *not*
17 “significantly predispose patients to arrhythmias.” Moreover, defendants had not provided
18 preclinical ECG data as requested by the FDA, as alleged in ¶84, and therefore did not have the pre-
19 clinical or clinical evidence to suggest that Ranexa did *not* “significantly pre-dispose patients to
20 arrhythmias.”

21 (d) Around this time, defendants received a discipline letter from the FDA
22 informing it of deficiencies in its NDA that needed to be addressed. At some point thereafter
23 defendants determined they would amend the NDA to address these deficiencies.

24 (e) The statements of July 17, 2003 pertaining to the QT interval were false when
25 made because there were scores of instances of QT prolongation above 20 milliseconds of
26 prolongation and 500 msec of interval, contrary to defendant Lange’s representations, as alleged in
27 ¶¶62-70.

28 **The Truth of the September 2003 Advisory Committee Meeting Emerge**

1 103. On August 1, 2003, the truth about the September 2003 Advisory Committee meeting
2 began to emerge. Defendants announced that the FDA Cardio Renal Advisory Committee would not
3 review Ranexa on September 15-16, 2003, claiming that this would not allow the FDA or the
4 Company to complete ongoing discussions regarding the Ranexa NDA. Defendants stated in their
5 August 1, 2003 press release:

6 CV Therapeutics (Nasdaq: CV Therapeutics) announced that it had reached
7 agreement today with the U.S. Food and Drug Administration (FDA) to cancel the
8 review of Ranexa(TM) (ranolazine) by the Cardiovascular and Renal Drugs Advisory
9 Committee in September 2003.

10 CV Therapeutics and the FDA agreed that a September advisory committee
11 meeting, which would have required a mid-August distribution of briefing packages
12 to advisory committee members, would not have provided sufficient time for CVT
13 and the FDA to complete ongoing discussions, communications and analyses of the
14 Ranexa NDA.

15 Ex. 43.

16 104. On this news, the Company's shares plummeted 26% to \$25.82 per share.

17 **False and/or Misleading Statements**

18 105. On August 4, 2003, defendants held a conference call to discuss the August 1, 2003
19 press release. The conference call was conducted by defendants Lange and Speigelman. In the call,
20 Lange stated:

- 21 • “On Friday, August 1, the FDA and CVT mutually agreed” that a September
22 advisory panel meeting “would not have provided sufficient time for either CVT or
23 the FDA to complete ongoing discussions, communications and analysis of the
24 Ranexa NDA – *more or less routine stuff* – in order to have an appropriate package
25 out by mid-August to the advisors.”
- 26 • “So what’s changed and what hasn’t? In fact, very little has changed other than the
27 September panel being cancelled.... We have not received any kind of non-approval
28 letter, **NOTHING**, for example, regarding QTC [sic] ... or other issues in that
regard....”
- “Now some details may be useful to describe, because this, obviously, is of interest
to many people. We actually have been very pleased with our level of disclosure
with the FDA.”
- “So far, for example, we have received detailed questions surrounding such areas as
statistical methods, preclinical methods, metabolism, toxicology and so forth. These
are not expected; they’re routine and we should be able to resolve them. But in view
of both the FDA and CVT, they do not make appropriate panel questions and we’d
have very a short time between today and mid-August for that panel package
preparation.”

- 1 • The delay was caused by the FDA's failure to complete its review of these issues and thus frame questions for the panel.
- 2 • "[W]e do not believe the news impacts the potential approvability of Ranexa in any way."
- 3
- 4 • The cancelled meeting was caused in part by the availability of the advisors.
- 5 • "Now I want everyone to remember, we still believe that we're going to launch Ranexa next year ... we're continuing with our commercial preparations to support the potential launch. Manufacturing runs are being completed to build inventory. We've recruited and are recruiting sales leadership, into district and regional sales force managers. We're conducting additional market research and pricing studies."
- 6
- 7
- 8 • In answer to an analyst's question, "[B]ut there's nothing in the process so far that makes you believe you need another study, is that correct?" Lange responded: "That's right. Exactly."
- 9

10 Ex. 27 (Conf. Call, Aug. 4, 2003).

11 **Reasons False and/or Misleading**

12 106. Defendants' statements in the conference call were false and/or misleading for the reasons set forth in "Defendants Hid Material Concerns About the QT Data," ¶¶62-66; "Defendants Failed to Disclose the FDA's Concerns Conveyed to Defendants, the Discipline Review Letter and the NDA Amendment," ¶¶67-70; "The FDA Notified Defendants that the QT Data Was Insufficient," ¶¶71-72; "Defendants Hid Other Material Deficiencies in the NDA," ¶73; "The Efficacy Data Was Deficient." ¶86. Most importantly, defendants omitted their failure to answer the FDA questions concerning pre-clinical studies, CV Therapeutics' receipt of a discipline letter outlining deficiencies in the NDA, and defendants' preparation of an amendment to the NDA, in response, which amendment was filed, in secret, on September 13, 2003. In addition, as set forth in the ¶69, the FDA was encouraging CV Therapeutics to perform another study so that Ranexa could be approved as a secondary-line of therapy for refractory angina patients. On September 5, 2003, defendants wrote to the FDA agreeing that such a study would be appropriate. See ¶69.

24 **False and/or Misleading Statement**

25 107. Defendants further misrepresented their QTc prolongation results in the Company's SEC Report on Form 10-Q filed August 14, 2003 for 2Q03. Defendants' only mention of any issue of QTc interval prolongation is buried among the risk factors:

28 For example, some drugs that prolong the electrocardiographic QT interval carry an increased risk of serious cardiac rhythm disturbances, or arrhythmias, while other
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1 drugs that prolong the QT interval do not carry an increased risk of arrhythmias.
 2 ***Small but statistically significant increases in the QT interval were observed in***
 3 ***clinical trials of Ranexa.*** However, the clinical significance of such changes
 remains unclear, and ***other clinical and preclinical data do not suggest that Ranexa***
significantly pre-disposes patients to arrhythmias....

4 108. On September 16, 2003, defendants obtained \$14.9 million in exchange for CV
 5 Therapeutics common stock under the equity line of credit.

6 109. On September 23, 2003, defendant Spiegelman made a presentation at the UBS
 7 Warburg Investor Conference. During that presentation, Spiegelman made further false and/or
 8 misleading statements pertaining to the frequency and magnitude of Ranexa's effect on QT interval
 9 prolongation. Defendant Spiegelman stated:

10 So, if you've been following the story, you also know that if you, the ---- if you will
 11 on Ran, the, the issue that, that definitely Wall Street has talked about and that we
 12 expect the regulators to at least pay attention to uh is ***the fact that Ran causes a***
 13 ***small but statistically significant and dose related increase in the QT interval*** which
 14 is this portion of the measurement on the electrocardiogram.... The uh in the whole
 15 database, in our 3,300 patients and we look at patients ***on drug levels that are***
 16 ***consistent with the drug levels that we're planning uh asking for approval for, 500***
 17 ***to, 1,000mg, that QTC [sic] effect is 2, a little over 2 for the 500mg and 5 for the***
 18 ***1,000mg.*** Um, typical drugs that, that cause the QT to go up and that have caused
 19 problems, Celbane [sic] sort of being the poster-child example of this ***had a QT***
 20 ***increase*** that was bigger in certain sub-groups, patients with congestive heart failure.
 21 ***Women,*** elderly patients or patients with low heart rate. The QT effect was all
 22 bigger on, on uh in those groups. In, in these drugs. ***That is not true in Ran,*** the 2 to
 23 5 is the same statistically ***in these sub-group as well.***

24 Ex. 44 (UBS Warburg Investor Conf., Sept. 23, 2003).

25 **Reasons False and/or Misleading**

26 110. Defendants' statements pertaining to the results of the QT interval prolongation data
 27 were false or misleading when made, for the reasons set forth in "Defendants Hid Material Concerns
 28 About the QT Data," ¶¶62-66; "Defendants Failed to Disclose the FDA's Concerns Conveyed to
 Defendants, the Discipline Review Letter and the NDA Amendment," ¶¶67-70; "The FDA Notified
 Defendants that the QT Data Was Insufficient," ¶¶71-72; "Defendants Hid Other Material
 Deficiencies in the NDA," ¶73; "The Efficacy Data Was Deficient." ¶86. In particular, defendants'
 statements pertaining to the studies of Ranexa on women were false when made because the studies
 conducted on women were deficient, such that both the FDA and Advisory Committee requested
 "future clinical studies" to address gender differences.

1 111. On October 3, 2003, CV Therapeutics filed a mixed-shelf registration statement
2 seeking to issue \$300 million in debt securities.

3 **False and/or Misleading Statements**

4 112. On October 23, 2003, CV Therapeutics announced that the FDA's Cardio Renal
5 Advisory Committee had scheduled its review of Ranexa on December 9, 2003. In response to this
6 news, CV Therapeutics' stock price rose from \$18.22 per share, on October 22, 2003, to \$22.45 per
7 share on October 23, 2003. Ex. 45 (Press Release, Oct. 23, 2003).

8 113. On October 30, 2003, after the close of the market, CV Therapeutics announced that
9 the FDA issued an "Approvable Letter" with conditions for Ranexa. Of this non-public letter, the
10 Company misrepresented the FDA's findings, and omitted material facts necessary to make the
11 statements, under the circumstances made, not false or misleading. The Company stated in its press
12 release:

13 In the approvable letter, the FDA indicated that *there is evidence that*
14 *Ranexa is an effective anti-anginal*, and that additional clinical information is
15 needed prior to approval. We understand that the FDA *may be prepared to*
reevaluate this requirement based on the results of the advisory committee review.
The FDA is not required to follow the recommendations of the advisory committee.

16 Ex. 28 (Press Release, Oct. 30, 2003).

17 114. On this news, the stock dropped 21.7%, losing \$4.89, and closing at \$17.63 per share
18 on October 31, 2003. However, the stock would have dropped even further had the true results of
19 the QT interval prolongation clinical studies been known to the public.

20 115. In follow-up conferences with analysts, defendants repeated their materially false and
21 misleading statements:

22 (a) Dennis Harp of Deutsche Bank issued an analyst report on October 31, 2003
23 which was based on and repeated statements from management. Specifically, Harp stated:

24 CV Therapeutics has presented some QTc data on Ranexa, although there has
25 not been a full disclosure of all QTc data to permit a more complete analysis.
Nonetheless, *based on what has been presented, we are optimistic* that Ranexa will
26 ultimately be approved by the FDA, and that approval could come in 1H04.

27 * * *

28 The maximum mean QTc prolongation at peak drug levels compared to
placebo was approximately 14 msec at a dose of 1,500 mg twice daily.... We believe

1 that based on the Phase III data from combination usage, the company will seek
 2 approval for a dose of 750 mg twice daily. The QTc prolongation at 750 mg twice
 3 daily in the CARISA trial was approximately 6 msec, although there is a slight
 variation in that estimate based on the correction factor used to adjust the QT to
 obtain the more generally used QTc.

4 Ex. 46 (Deutsche Bank, Oct. 31, 2003).

5 (b) Dennis Harp of Deutsche Bank issued another analyst report on November 3,
 6 2003 which was based on and repeated information obtained from management. Harp specifically
 7 stated:

8 After speaking with management, we are of the impression that the issued letter was
 9 non-committal toward additional studies than the market has initially reflected, and
 believe that the expert advisory panel could decide that enough data have been
 submitted to reach a conclusion on the overall risk-benefit profile of the drug.

10 Ex. 47 (Deutsche Bank, Nov. 3, 2003).

11 116. On November 12, 2003, the Company issued its SEC Form 10-Q for 3Q03, which
 12 included false and misleading statements and omitted material facts, in order to make the statements
 13 made, in light of the circumstances under which they were made, not misleading. Specifically, of
 14 the Approvable Letter and the QT prolongation data, defendants stated:

15 In the approvable letter, *the FDA indicated that there is evidence that Ranexa is an*
 16 *effective anti-anginal*, and that additional clinical information is needed prior to
 17 approval.... We understand that the FDA may be prepared to reevaluate the
 18 requirement for additional clinical information prior to approval based on the results
 of the advisory committee review. The FDA is not required to follow the
 recommendations of the advisory committee.

19 * * *

20 *Small but statistically significant mean increases in the QT interval were observed*
 21 *in clinical trials of Ranexa.... The clinical significance of the changes in QTc*
 22 *interval observed in clinical trials of Ranexa remains unclear, and other clinical*
and preclinical do not suggest that Ranexa significantly pre-disposes patients to
arrhythmias....

23 **Reasons False and/or Misleading**

24 117. Defendants' statements pertaining to the effect of the FDA Approvable Letter and the
 25 QT prolongation data were false and/or misleading when made because "Defendants Hid Material
 26 Concerns About the QT Data," ¶¶62-66; "Defendants Failed to Disclose the FDA's Concerns
 27 Conveyed to Defendants, the Discipline Review Letter and the NDA Amendment," ¶¶67-70; "The
 28 FDA Notified Defendants that the QT Data Was Insufficient," ¶¶71-72; "Defendants Hid Other

1 Material Deficiencies in the NDA,” ¶73; “The Announcement of the Sept. 15, 2003 Advisory
2 Committee Meeting Was Misleading,” ¶¶74-84; “Defendants Failed to Disclose Material Portions of
3 the Approvable Letter,” ¶85; “The Efficacy Data Was Deficient.” ¶86: (i) at the time that these
4 statements were made, defendants were aware that the FDA’s Approvable Letter was much more
5 critical than represented to investors (*See* ¶85); (2) the FDA had requested additional pre-clinical
6 studies data related to QT prolongation which the Company failed to provide (*see* ¶¶67-72); and (3)
7 the QT prolongation data was much worse then characterized. (*See* ¶¶62-66).

8 **The Truth Is Partially Disclosed**

9 118. As is standard procedure, on December 8, 2003, on the eve of the Advisory
10 Committee Meeting, the FDA released all of the data which it had provided to the Cardio-Renal
11 Advisory Committee in support of its analysis and position on Ranexa. Moreover, the FDA released
12 its October 30, 2003 Approvable Letter along with the questions which the FDA posed to the
13 Advisory Committee. Many of these documents were made available to the public via Internet.
14 These documents revealed that the FDA had serious concerns about the efficacy and safety of
15 Ranexa, particularly as it relates to an increase in the QT interval. These concerns were much more
16 serious than defendants had represented. Moreover, the FDA medical reviewers noted on several
17 occasions, in the briefing material, that the Company had failed to provide critical ECG data in both
18 the dog studies and the pre-clinical studies. *See* ¶¶71-72.

19 (a) According to the FDA Director of the Division of Cardio-Renal Drug
20 Products, Douglas C. Throckmorton, M.D. and as revealed in the FDA’s Divisional Memorandum
21 dated October 28, 2003, “[r]anolazine [Ranexa] ... has sufficient safety concerns to warrant
22 additional studies prior to approval. The safety concerns are two-fold: (1) Delayed cardiac
23 repolarization, manifest by prolongation of the QT interval....” Ex. 24 at 1 (Divisional
24 Memorandum, Oct. 28, 2003).

25 (b) Dr. Throckmorton of the FDA also concluded, “[i]n the end, for a drug like
26 [R]anolazine [Ranexa], the available efficacy data are modest at best, and are simply insufficient
27 to bear [on] any significant safety concerns.” *Id.* at 2.

1 (c) Dr. Throckmorton further concluded that “*much of the animal work was*
2 *done using a lower standard of quality than is now in place,*” such that while, “[n]o clear signal of
3 *concern regarding changes in the QT interval can be found in the standard cardiac evaluations of*
4 *the animals ... methodological flaws prevent this from being reassuring.*” *Id.* at 3-4.

5 (d) In his memo on September 3, 2003, John Koerner, Ph.D. of the FDA
6 commented that *there was no ECG data provided in connection with the non-clinical studies* (this,
7 despite the fact that the FDA had made clear in its opinion papers that it would look to non-clinical
8 data in analysis of drugs that prolong QT interval, *see* ¶38). Koerner notes that *CV Therapeutics*
9 *was asked to provide this data, and on July 2, 2003, CV Therapeutics responded that the ECG*
10 *data was unavailable.* Ex. 23 at iii (Koerner report, Executive Summary).

11 (e) FDA Medical Reviewer Shari L. Targum, M.D. and Statistical Reviewer
12 Valeria Freidlin, Ph.D. concluded that “[t]here are no studies in this submission demonstrating
13 *superiority of ranolazine over another anti-anginal medication.*” Ex. 25 at 2 (Integrated Summary
14 of Efficacy).

15 119. In fact, the documentation revealed that the FDA did not even ask the Advisory
16 Committee to address the approvability of Ranexa; rather, the Committee was simply asked to
17 “opine on the next steps in the Ranexa clinical development program.” Ex. 26 (Cardiovascular and
18 Renal Drugs Advisory Committee Meeting, Committee Questions, Dec. 9, 2003).

19 120. Following the release of the FDA documents, analysts reacted negatively. On
20 December 8, 2003, David Webber of First Albany lowered his rating from Buy to Neutral, stating:

21 *We are lowering our rating to Neutral from Buy on negative FDA briefing
22 documents for tomorrow’s FDA advisory panel review of Ranexa, implying that it is
unlikely that Ranexa can be approved without a substantial new clinical trial.

23 *In the documents, the FDA appears to view Ranexa as *modestly effective*, but notes
24 *significant safety risks* that are not offset by the product’s demonstrated benefits.

25 *The documents disclose several issues, including dose-response, *lack of efficacy in*
26 *women, insufficiency of safety database, and high QTc prolongation in patients*
with impaired liver function, among others, *that have not previously been revealed.*

27 Ex. 48 (First Albany, Dec. 8, 2003).

1 121. Also on December 8, 2003, Akhter Samad, M.D., Ph.D. of Bear Stearns issued a
 2 report going into depth about the material deficiencies revealed in these FDA papers regarding the
 3 Baneto studies:

4 This morning the FDA posted the briefing documents along with the
 5 Approvable Letter for CV Therapeutics' drug, Ranexa, indicated for chronic angina
 6 and scheduled to be reviewed by the Cardiovascular and Renal Drugs Advisory
 7 Committee tomorrow ... [i]ssues raised by the FDA primarily focused on dosing,
 8 efficacy, and safety. We believe that these issues (described in detail below) will
 9 likely lead the Panel to request additional studies....

10 1) Dosing and efficacy issues:

11 The FDA noted:

12 A) "evidence that ranolazine is an effective anti-anginal drug." The trials,
 13 however, ***do not adequately characterize the relationship between dose and
 14 therapeutic effect*** sufficiently to provide labeling instructions."

15 B) "great inter-subject variability in plasma levels and ***the small number of
 16 studies exploring the does range for ranolazine in patients with angina*** making it
 17 difficult to adequately describe in labeling how ranolazine should be used."

18 C) The absence of a compelling dose response in study CVT3033 (parallel group
 19 12 week study), as well as "interpretability issues in study CVT3031 (wherein) the
 20 reviewers could not conclude a statistically significant treatment effect at trough
 21 using first period data." In the August 2002 pre-NDA meeting, the FDA noted that
 22 "in CVT3033, patients did not receive an adequate doses of amlodipine, atenolol and
 23 diltiazem and, therefore, interpretation of ranolazine's effect as an add-on therapy
 24 was difficult." In addition, "a consumption was seen in (only) one study
 25 (CVT3033)." As a result of these concerns, the FDA concluded that ***results of the
 26 clinical studies do not support the proposed labeling***, which gives a starting doses of
 27 500mg bid with upward titration through 750mg bid to 1000mg bid, as needed, based
 28 on clinical response."

* * *

29 The FDA concluded that ***unresolved efficacy issues*** include: 1) efficacy of
 30 ranolazine when added to maximal doses of anti-anginals; 2) comparisons to ...
 31 exploration of dose-response relationship such that efficacy at lower doses ... are
 32 identified; in addition, ***efficacy in women should be explored.*** The latter point was
 33 a reference to the FDA's observation of "a smaller effect of ranolazine in women
 34 with angina," wherein "exercise duration in women ... is reduced to between 28%
 35 and 42% of that in men...."

36 With respect to special populations (apart from the gender issue noted above),
 37 the FDA reviewer also noted that the "the study population in studies 3033 and 3031
 38 was over 90% Caucasian. There were insufficient numbers of non-Caucasians to
 39 provide a meaningful analysis of racial/ethnic differences."

40 2) 3 major safety issues:

1 A) “Potential testicular toxicity, manifested as impaired fertility in rats...” The
 2 FDA also noted that the “available data are inadequate to determine whether this was
 a chance finding or evidence of testicular toxicity by ranolazine.” *We note that this
 safety issue was not apparent to us in our previous analyses of available data.*

3 B) QT prolongations: “an effect on the QT interval was seen in all patient
 4 populations studied ... and you have *neither provided sufficient rationale for
 discounting this as a potential concern* nor devised dosing strategies that would
 5 avoid significant QT prolongation in some patients.” With respect to the latter issue,
 the FDA makes reference to *patients with hepatic (liver) impairment* and those
 6 taking inhibitors of the cytochrome oxidase enzyme CYP3A4 “*where larger effects
 on the QT interval were seen or can be expected.*”

7 The FDA also stated: “*given the availability of other anti-anginal drugs
 8 that do not prolong the QT interval, there needs to be a clear reason to approve a
 therapy with what appears to be an additional, possibly life-threatening risk.*” The
 9 FDA reviewer also stated: “*we are not convinced* by the available data that the
 effects of ranolazine on QT interval *would not lead to increased risk of arrhythmias*
 10 at doses and in populations where it is likely to be used.” We remain especially
 11 concerned about the lack of larger studies involving supra-therapeutic doses of
 ranolazine, involving a direct measurement of QT prolongation.

12 C) Safety database: the FDA reviewer indicated that “*the present database has
 13 information fewer than 1,000 patients given relevant doses* of ranolazine for at least
 one month, an exposure well below what is typically expected for chronic treatment
 14 for a symptomatic claim.” Given the large (6 million patients) and complex patient
 spectrum in chronic angina (patients with heart failure, diabetes, chronic obstructive
 lung disease etc), we believe this is an important issue....”

15 Ex. 49 (Bear Sterns, Dec. 8, 2003).

16 122. Based on these new revelations, CV Therapeutics stock fell \$4.55 per share or 27%,
 17 on December 8, 2003, closing at \$12.21 per share.

18 123. On December 9, 2003, the FDA Cardio-Renal Advisory Committee reviewed Ranexa.
 19 During the review, the Committee members raised issues pertaining to several deficiencies in the
 20 Ranexa NDA, including aspects of the QT interval prolongation caused by Ranexa. Critical
 21 comments also were made regarding the Company’s failure to conduct studies on a diverse
 22 population. As reported by Bear Stearns analyst, Akhter Samad, M.D., Ph.D., on December 10,
 23 2003:

24 [T]he primary issues that concerned the Panel included: 1) the small proportion of
 25 females ... 2) limited ethnic/racial diversity ... and 3) a lack of patients who were
 26 refractory to existing anti-anginals or not treated with the maximum tolerated dose of
 existing, anti-anginals in the CARISA study.

27 * * *

1 We are downgrading CVTX [CV Therapeutics] to an Underperform from a
 2 Peer Perform based on the following considerations: 1) our belief that in order to
 3 obtain approval of Ranexa the Company will likely have to conduct a study in a
 4 racially/gender-diverse, and possibly “resistant” angina population, and with an
 5 uncertain outcome with regard to efficacy (compared to previous phase III trials
 involving non-diverse patients who were treated with sub-maximal doses of just one
 anti-angina therapy); 2) a timeline for completion of such a study of roughly 12-24
 months, which could result in a delay in the drug’s approval until 2006 or later....

6 Ex. 8 (Bear Sterns, Dec. 10, 2003).

7 124. Other analysts have stated that additional studies will likely delay the launch of
 8 Ranexa, if it is ultimately approved, by several years. Eric Schmidt at SG Cowen has stated that “the
 9 additional studies will likely delay the commercial launch of Ranexa by two years, from the second
 10 quarter of 2004 to the second quarter of 2006.”

11 125. Still other analysts were angered over CV Therapeutics’ incomplete and misleading
 12 disclosures. Stephen V. Cullen of White Mountain Capital wrote in his December 12, 2003 analyst
 13 report:

14 [T]he company should also be taken to task for its insistence on applying for
 15 approval in an unrestricted population, as well as its *incomplete (and misleading)*
 16 *disclosure of information* to the investment community.

17 Ex. 10 (White Mountain Capital, Dec. 12, 2003). Today CV Therapeutics stock hovers around
 18 \$14.00 to \$15.00 per share.

19 INSIDER TRADING

20 The following chart shows the Individual Defendants’ sales of their CV Therapeutics stock
 21 both before and during the Class Period, showing the value of an inflated stock price to the
 22 defendants:

23 Sales Transactions	Shares	price	gross proceeds	exercise price	exercise cost	Net Proceeds
24 Blackburn						
11/19/2001	4000	\$53.95	\$215,800.00	\$9.00	\$36,000.00	\$179,800.00
5/30/2003	6000	\$30.62	\$183,721.20	\$9.00	\$54,000.00	\$129,721.20
5/30/2003	3710	\$31.66	\$117,449.70	\$0.00	\$0.00	\$117,449.70
27 Class Period Total	9710		\$301,170.90			

1	Lange						
	11/19/2001	5000	\$53.95	\$269,750.00	\$7.50	\$37,500.00	\$232,250.00
2	11/19/2001	5000	\$53.95	\$269,750.00	\$7.50	\$37,500.00	\$232,250.00
	12/26/2001	3000	\$54.76	\$164,271.99	\$7.50	\$22,500.00	\$141,771.99
3	12/27/2001	2000	\$53.92	\$107,840.00	\$7.50	\$15,000.00	\$92,840.00
	12/28/2001	1000	\$54.11	\$54,110.00	\$7.50	\$7,500.00	\$46,610.00
4	12/31/2001	1000	\$52.08	\$52,080.00	\$7.50	\$7,500.00	\$44,580.00
	1/10/2002	1000	\$51.08	\$51,078.00	\$7.50	\$7,500.00	\$43,578.00
5	1/11/2002	1000	\$51.78	\$51,781.00	\$7.50	\$7,500.00	\$44,281.00
	2/28/2002	6000	\$40.43	\$242,605.02	\$7.50	\$45,000.00	\$197,605.02
6	6/24/2002	7000	\$18.21	\$127,501.50	\$5.81	\$40,687.50	\$86,814.00
7	8/16/2002	3000	\$26.91	\$80,730.00	\$0.00	\$0.00	\$80,730.00
		35000		\$1,471,497.51			
8							
	3/19/2003	10000	\$17.46	\$174,587.00	\$5.81	\$58,125.00	\$116,462.00
9	5/12/2003	5000	\$19.51	\$97,541.50	\$5.81	\$29,062.50	\$68,479.00
	5/27/2003	5000	\$26.89	\$134,449.00	\$5.81	\$29,062.50	\$105,386.50
10	5/30/2003	5000	\$31.19	\$155,941.00	\$5.81	\$29,062.50	\$126,878.50
	6/6/2003	5000	\$40.51	\$202,537.00	\$5.81	\$29,062.50	\$173,474.50
11	Class Period						
	Total	30000		\$765,055.50			
12							
	Speigelman						
13	12/6/2001	5000	\$59.05	\$295,227.00	\$9.00	\$45,000.00	\$250,227.00
	3/15/2002	5000	\$40.73	\$203,650.00	\$9.00	\$45,000.00	\$158,650.00
14	8/22/2002	5000	\$28.74	\$143,717.70	\$5.81	\$29,062.50	\$114,655.20
		15000		\$642,594.70			
15							
	5/12/2003	5000	\$19.71	\$98,550.00	\$5.81	\$29,062.50	\$69,487.50
16	5/30/2003	6000	\$31.40	\$188,422.20	\$5.81	\$34,875.00	\$153,547.20
17	Class Period						
	Total	11000		\$286,972.20			

NO STATUTORY SAFE HARBOR

126. The statutory safe harbor provided for forward-looking statements under certain instances does not apply to any of the allegedly false statements pleaded in this Complaint. The specific false statements pleaded herein were not identified as “forward-looking statements” when made. Nor was it stated with respect to any of the statements forming the basis of this Complaint that actual results “could differ materially from those projected.” To the extent there were any forward-looking statements, there were no meaningful cautionary statements identifying important factors that could cause actual results to differ materially from those in the purportedly forward-looking statements. Alternatively, to the extent that the statutory safe harbor does apply to any forward-looking statements pleaded herein, defendants are liable for those false forward-looking

1 statements because at the time each of those forward-looking statements was made the particular
2 speaker knew that the particular forward-looking statement was false, and/or the forward-looking
3 statement was authorized and/or approved by an executive officer of CV Therapeutics who knew
4 that the statement was false when made.

5 **FIRST CLAIM FOR RELIEF**

6 **For Violation of Section 10(b) of the 1934 Act and Rule 10b-5**
7 **Against All Defendants**

8 127. Plaintiff incorporates ¶¶1-126 by reference.

9 128. During the Class Period, defendants disseminated or approved the false statements
10 specified above, which they knew or deliberately disregarded were misleading in that they contained
11 misrepresentations and failed to disclose material facts necessary in order to make the statements
12 made, in light of the circumstances under which they were made, not misleading.

13 129. Defendants violated §10(b) of the 1934 Act and Rule 10b-5 in that they:

14 (a) Employed devices, schemes, and artifices to defraud;

15 (b) Made untrue statements of material facts or omitted to state material facts
16 necessary in order to make the statements made, in light of the circumstances under which they were
17 made, not misleading; or

18 (c) Engaged in acts, practices, and a course of business that operated as a fraud or
19 deceit upon plaintiff and others similarly situated in connection with their purchases of CV
20 Therapeutics' publicly-traded securities during the Class Period.

21 130. Plaintiff and the Class have suffered damages in that, in reliance on the integrity of
22 the market, they paid artificially inflated prices for CV Therapeutics' publicly-traded securities.
23 Plaintiff and the Class would not have purchased CV Therapeutics' publicly-traded securities at the
24 prices they paid, or at all, if they had been aware that the market prices had been artificially and
25 falsely inflated by defendants' misleading statements.

26 131. As a direct and proximate result of these defendants' wrongful conduct, plaintiff and
27 the other members of the Class suffered damages in connection with their purchases of CV
28 Therapeutics' publicly-traded securities during the Class Period.

1 **SECOND CLAIM FOR RELIEF**

2 **For Violation of Section 20(a) of the 1934 Act**
3 **Against All Defendants**

4 132. Plaintiff incorporates ¶¶1-131 by reference.

5 133. Defendant CV Therapeutics and the Individual Defendants acted as controlling
6 persons of CV Therapeutics within the meaning of §20(a) of the 1934 Act. By reason of their
7 positions as officers and/or directors of CV Therapeutics, and their ownership of CV Therapeutics
8 stock, the Individual Defendants had the power and authority to cause CV Therapeutics to engage in
9 the wrongful conduct complained of herein. CV Therapeutics controlled each of the Individual
10 Defendants and all of its employees. By reason of such conduct, the Individual Defendants and CV
11 Therapeutics are liable pursuant to §20(a) of the 1934 Act.

12 **CLASS ACTION ALLEGATIONS**

13 134. Plaintiff brings this action as a class action pursuant to Rule 23 of the Federal Rules
14 of Civil Procedure on behalf of all persons who purchased CV Therapeutics' publicly-traded
15 securities (the "Class") on the open market during the Class Period. Excluded from the Class are
16 defendants.

17 135. The members of the Class are so numerous that joinder of all members is
18 impracticable. The disposition of their claims in a class action will provide substantial benefits to
19 the parties and the Court. CV Therapeutics had more than 28 million shares of stock outstanding,
20 owned by hundreds if not thousands of persons.

21 136. There is a well-defined community of interest in the questions of law and fact
22 involved in this case. Questions of law and fact common to the members of the Class which
23 predominate over questions which may affect individual Class members include:

- 24 (a) Whether the 1934 Act was violated by defendants;
- 25 (b) Whether defendants omitted and/or misrepresented material facts;
- 26 (c) Whether defendants' statements omitted material facts necessary to make the
27 statements made, in light of the circumstances under which they were made, not misleading;
- 28

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WITNESS INTERVIEWS

1
2 The factual allegations in the Complaint rely in part on the testimony of four independently
3 interviewed witnesses. These witnesses prefer that their identities not be publicly disclosed at this
4 point in the litigation. They fear direct retaliation from CV Therapeutics and the Individual
5 Defendants, as well as being “blackballed” within the biotechnology and pharmaceutical industries.
6 The witnesses are former employees and independent contractors of CV Therapeutics. All of the
7 witnesses had direct access to information that supports the statements contained in the Complaint,
8 and their accounts directly corroborate the independent testimony of one another. Their statements
9 contain sufficient detail to demonstrate their reliability.

CW1

10
11 1. CW1 was a Vice President of Clinical Research prior to and during part of the Class
12 Period at CV Therapeutics' Palo Alto headquarters. CW1 reported to Sandy Skettino, Vice President
13 of Clinical Research and Operations. Skettino reported to Andy Wolff, Senior Vice President of
14 Clinical Research and Development.

15 2. CW1 discussed in detail the monthly meetings which were chaired by Andy Wolff,
16 CV Therapeutics' Senior Vice President of Clinical Research and Development. Technically,
17 Wolff's meetings were to take place once a month, but according to CW1, they rarely happened on a
18 monthly basis. CW1 surmised that the frequency of these “monthly meetings” was closer to once
19 every two months.

20 3. CW1 said that the meetings were simply referred to as “Andy Wolff's Staff
21 Meetings.” Wolff would have a meeting agenda prepared and pre-circulated before every meeting.
22 An administrative assistant by the name of Judy Morgan prepared the agendas, and also recorded
23 and distributed the minutes for these meetings.

24 4. The participants/attendees at Andy Wolff's Staff Meetings typically included the
25 following individuals among others:

26 Sandy (Sandra) Skettino – Vice President of Clinical Research and Operations
27 Whedy Wang - Head of Statistics
28 Arlene Noodleman – Vice President of Marketed Products
Colin Hislop – Vice President of Clinical Research
Markus Jerling – Vice President of Clinical Research

1 Atul Laddu – Vice President of Clinical Research
2 Rafael Escandon - Senior Director of Clinical Operations

3 5. CW1 recalled one of these staff meetings in which QT prolongation was listed on the
4 agenda. Markus Jerling gave a presentation on his QT prolongation studies/research, and after the
5 presentation, CW1 said that Wolff proclaimed “Oh boy, we need to work on this!” Jerling agreed
6 that he would continue to work on the QT problem. CW1 believed that this meeting took place in
7 approximately November/December 2002 (before the NDA submission).

8 6. CW1 recalled that after this particular meeting, Judy Morgan left Wolff’s comments,
9 and the discussions about QT prolongation problems with Ranexa, out of the meeting minutes.

10 7. CW1 recalled that the Drug Information Association (DIA) hosted a meeting in
11 Puerto Rico in the fall of 2002 to discuss the clinical relevance of QT prolongation. CW1 did not
12 attend this meeting, but he said both Markus Jerling and Luiz Belardinelli (Vice President of Drug
13 Research and Pharmacological Sciences), were in attendance.

14 8. CW1 believed that most of the industry people attended this meeting, and said that
15 FDA representatives came to the meeting and made a presentation.

16 9. Upon returning from this DIA meeting, Belardinelli was very worried. Belardinelli
17 said “I don’t think this looks good for us.” Belardinelli’s statement was directly in reference to the
18 QT prolongation problems CV Therapeutics was facing with Ranexa.

19 10. Lange held his own staff meetings. He said Wolff, Belardinelli, Blackburn (Senior
20 Vice President of Drug Discovery and Pre-clinical Development), and Dan Speigelman (Senior Vice
21 President and Chief Financial Officer) attended Lange’s meetings.

22 11. In approximately June or July 2002, CW1 spent about two weeks reviewing the
23 approximately 200-page SBA draft. While reviewing the draft, CW1 recalled seeing “unusually
24 high” incidents of QT prolongation. When asked what exactly was unusually high, CW1 responded
25 that the incidents and intensity of QT prolongation were high. Although CW1 could not recall the
26 numbers of incidents that s/he believed to be high, s/he did state that he had compared the numbers
27 to another drug s/he had worked on. CW1 stated that the other had high incidents of QT
28

1 prolongation – so high, in fact, that s/he said s/he “killed the drug.” CW1 said Ranexa’s numbers
2 were similar enough so that it concerned CW1.

3 12. After reviewing the SBA draft, CW1 told an employee working on the SBA that from
4 CW1’s experience, the numbers in the clinical studies were very high – to the point that they would
5 raise a red flag. CW1 recalled that s/he made comments on the SBA draft to the effect that “the
6 intensity and incidents are high – this needs to be looked into carefully because the numbers are
7 going to raise a red flag.”

8 13. CW1 said that in August or September of 2002, s/he had a conversation with Jerling
9 about the SBA draft s/he had reviewed. S/he asked Jerling what they were going to do about the
10 intensity and incidents of QT prolongation in the Ranexa studies. CW1 said that Jerling’s response
11 was to the effect that, “I know the numbers are high; we need to work on it to see how to improve
12 the numbers.”

13 14. CW1 did not believe that there was a legitimate way to improve the QT prolongation
14 numbers reflected on the SBA draft.

15 15. CW1 believed that Jerling was using various techniques of calculating or
16 “massaging” the numbers to gain more favorable results. CW1 recalled that during one of Wolff’s
17 staff meetings, Wolff asked Jerling, “How are we doing on the QT project?” Markus’ reply was that
18 he was applying different techniques to calculate the QT prolongation numbers.

19 16. CW1 was informed that Jerling submitted his resignation to CV Therapeutics. It has
20 not yet been determined when Jerling left, or if he has left, but according to CW1, Jerling was
21 resigning as a result of dissatisfaction with CV Therapeutics’ upper management.

22 17. CW1’s own observations were that if a drug is to be used across the board, or across
23 all populations (African American, Asian, Latino, etc.), then it needs to have adequate testing and
24 exposure to all of these populations. CW1 said the sub-patient population needed to be exposed to
25 the testing, as this is a routine practice and an industry standard. If adequate exposure is not given to
26 all populations (as in the Ranexa study) then this is “very negative” and not a comprehensive study.

1 18. CW1 again confirmed that approximately 10 to 15 patients participating in the
2 Ranexa study tested higher than 500 msec between their QT waves, a number which, according to
3 CW1, made him/her extremely nervous.

4 19. CW1 also stated that s/he did recall instances of patients who experienced QT
5 prolongation in excess of 30 msec.

6 20. CW1 brought the fact that the QT prolongation looked very high to the attention of
7 Jerling prior to the filing of the NDA. Jerling agreed that the numbers were high and that they
8 “needed to do something” to lower these numbers for approval.

9 21. According to CW1, a Director of Clinical Research, during the Class Period,
10 discussed with CW1 the QT prolongation problems on a daily basis. This Director told CW1 that
11 s/he was asked to analyze the data in a manner which would reflect that QT prolongation was not a
12 significant factor with Ranexa. CW1’s report told CW1 that s/he was told to “re-analyze” the
13 number. Specifically, CW1’s report explained that Jerling told him/her to have the statisticians re-
14 analyze the incidents and magnitude of the QT prolongation.

15 CW2

16 1. CW2 was the Director of Clinical Research until August 2003 at CV Therapeutics'
17 Palo Alto headquarters. CW2 was responsible for clinical research on the drugs CVT-3146 and
18 CVT-510. CW2 did not specifically work on Ranexa. CW2 reported directly to Atul Laddu, a
19 former Vice President of Clinical Operations. CW2 resigned from CV Therapeutics.

20 **Summary of Interview**

21 2. CW2 confirmed that there were numerous meetings in 2002 regarding the QT
22 problems with Ranexa. Vice-President level and above executives attended the meetings. CW2
23 didn't attend but noted when the meetings occurred. CW2 felt that it was misleading for CV
24 Therapeutics executives to state publicly that they had no worries about the QT problem when they
25 were having frequent meetings specifically about the problem.

26 3. CW2 explained that the original clinical studies done in the United Kingdom on
27 Ranexa indicated that there were potential issues with QT prolongation. CW2 was also aware of the
28 QT prolongation problems with Ranexa partly because QT prolongation was also an issue with the

1 drugs CW2 was researching. Because of this, CW2 reviewed some of the QT prolongation data on
2 Ranexa in conjunction with CW2's own research. Also, the data management and the statistics
3 group worked on all of the projects at CV Therapeutic. Therefore, many of the same people working
4 on Ranexa also worked on the drugs that CW2 researched.

5 4. CW2 disclosed that there was a lot of debate at CV Therapeutic on whether to
6 conduct additional clinical studies on Ranexa specifically related to the QT prolongation issue.
7 Andy Wolff, Vice President of Clinical Research and Development, was in charge of the NDA
8 submission for Ranexa. Some of the Vice Presidents at CV Therapeutics adamantly believed that
9 additional clinical studies on QT prolongation with Ranexa should be done before the NDA was
10 submitted. However, Wolff refused to do any additional studies and decided to submit the NDA
11 without them. A Vice President came up to CW2 after the NDA was filed and expressed his/her
12 frustration that it was filed without additional data on QT prolongation. These people felt that the
13 NDA didn't adequately address the problem. CW2 declined to give this Vice President's name.

14 5. Jerling, Vice President of Clinical Research, created the mathematical models of all
15 the data involving QT issues with Ranexa. Jerling was the person responsible for studying QT
16 prolongation with Ranexa. He also created the models for the drugs CW2 was working on. Because
17 of this, CW2 often went to Jerling to figure out what to do with QT prolongation issues. CW2
18 learned of the QT issues with Ranexa because these same issues surfaced with the drugs CW2 was
19 working on.

20 6. The QT data is derived from a mathematical formula which has many different
21 variables. CW2 stated that CV Therapeutics tried to "correct" the QT problem with Ranexa in the
22 NDA by blaming other variables in the formula such as gender, age, ventricle index and diabetes
23 factors. They also used correction formulas or factors and pooled analysis to "correct" the QT
24 problem. This was done to make it appear that the QT prolongation was caused by other factors and
25 not the drug itself. CW2 stated that this was the "strategy" that CV Therapeutics used to lessen the
26 impact of the QT problem on Ranexa. CW2 is not aware of the exact numbers that were involved,
27 only the method that was used. CW2 was told that this was the strategy that was used for Ranexa
28 and would also be used for the two drugs CW2 was studying. A few people in data management

1 would generate the data for Ranexa and if they raised any questions they would be immediately be
2 moved to other projects.

3 7. CW2 believes that the September 2003 Ranexa review meeting was cancelled
4 because CV Therapeutics wanted more time to respond to QT prolongation questions from the FDA.
5 The FDA wanted more information about the QT problem. CW2 thinks that the executives at CV
6 filed the NDA for Ranexa knowing that it would probably not pass because of the QT problems but
7 decided to gamble and hope it would not become a bigger issue. However, the FDA did catch onto
8 the problem and began to ask detailed questions regarding QT prolongation in March. Defendants
9 then cancelled the meeting to try to gain more time to gather their resources.

10 8. CW2 said that all of the Ranexa questions from the FDA from March 2003 forward
11 concerned QT prolongation. There was a letter from the FDA to CV Therapeutics in March that said
12 they were going to start reviewing in depth the NDA filing for Ranexa.

13 **CW3**

14 1. CW3 was the Associate Director of Clinical Data Management until late spring at CV
15 Therapeutics' Palo Alto headquarters. CW3 was responsible for arranging the data that was used for
16 Ranexa's NDA submission to the FDA. CW3 managed three Clinical Data Managers, six SAS
17 programmers and two Clinical Data Assistants. CW3 also acted as a liaison between the
18 Biostatistics group and the Regulatory Affairs Department.

19 2. CW3 explained that 65 studies of Ranexa were tabulated in the NDA that was
20 submitted to the FDA. One measurement taken in these studies is the QTc interval time of patients
21 taking Ranexa. CW3 believes this measures the amount of time a patient's heart is slowed down by
22 the drug. The longer this time period, the more dangerous the drug is.

23 3. CW3 disclosed that the QTc measurement data included in Ranexa's NDA was
24 "manipulated" to make it appear that the data was more favorable than it really was. The data was
25 manipulated across the 65 studies in the analysis that was filed. Ranexa's QTc measurements were
26 longer than what was considered safe. This means that Ranexa has the potential to cause adverse
27 reactions in patients. CW3 said that Vice President level executives and above knew about the QTc
28 problem with Ranexa. CW3 says s/he knows one or two statisticians that were aware of this as well.

1 4. CW3 explained that s/he, along with other people at the Company, knew there was a
2 problem with the QTc values at least as early as November 2002. CW3 coordinated the entire NDA
3 submission process. CW3 supervised the data managers and the Statistical Analysis Software
4 ("SAS") programmers. Alec Vardy was in charge of the NDA submission, but CW3 did all the
5 actual work putting the package together for the FDA.

6 5. During the process of preparing the NDA for submission, CW3's department was
7 often asked to re-do data they had previously submitted to the Regulatory Affairs Department. CW3
8 was repeatedly told that, "the values are off." CW3 later realized that this was the QTc data that was
9 being changed and reinserted into the NDA. CW3 said that it was the statistical group that actually
10 altered the QTc data, CW3's group just re-loaded the revised data into the NDA.

11 6. CW3's department was under constant pressure to get the NDA submitted on time.
12 The programmers and data managers were very upset that they were being asked to continually re-do
13 the data. They didn't know why the numbers were changing, just that there was some problem.
14 CW3 said that management told him/her and his/her department that they had left some key data out
15 that needed to be included. CW3 said the manipulated data was coming to him/her as data that
16 his/her group had failed to include in the NDA. The manipulated data came from the statistical
17 group. Whedy Wang was the head of the statistical group and knew about the manipulated data.

18 7. CW3 was told by current CV Therapeutics employees that the FDA cancelled the
19 scheduled September 2003 Ranexa review meeting when they discovered that the QTc data in the
20 NDA was not correct. The FDA performed a "reverse analysis" of the data and determined that the
21 QTc numbers didn't add up. In other words, the FDA backtracked from the conclusions in the NDA
22 and discovered that the data wasn't correct. The FDA told defendants that they didn't like how the
23 numbers were computing and asked them to perform an interim analysis. The FDA said the review
24 meeting might be rescheduled for December 2003.

25 8. CW3 received an influx of voicemails from current employees at CV Therapeutics
26 explaining why the FDA cancelled the meeting. Will Taucher, a statistician, called CW3 and told
27 him/her that the FDA cancelled the meeting because of the QTc issue. Another current employee
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1 named Ted (CW3 couldn't remember his last name) also told CW3 that this was the reason the FDA
2 cancelled the meeting.

3 9. CW3 explained that a company submitting an NDA never knows how much scrutiny
4 the FDA will do of the numbers. Sometimes the FDA starts at the end and goes back over the
5 numbers or starts at the middle and goes back. However, the FDA would only cancel a scheduled
6 meeting for serious reasons.

7 10. According to CW3, even if the FDA approves Ranexa with the QTc value problem,
8 doctors still won't want to use it. Doctors will not think the drug is safe with the problem.
9 Therefore, CV Therapeutics has another reason besides the FDA approval to keep the QTc problem
10 from being known. Doctors will view Ranexa with QTc problems as not any more valuable than
11 current drugs for Angina and will avoid it.

12 **CW4**

13 1. CW4 is an independent contractor who oversaw the data compilation of the Ranexa
14 project at CV Therapeutics. CW4 is a computer programmer specializing in SAS and worked in that
15 capacity on the Ranexa project. According to CW4, the Company's excuse for canceling the
16 September 2003 meeting with the FDA Advisory Committee was false. CW4 claimed that the data
17 and information was all prepared and ready to go for the Advisory Committee. Rather, CW4
18 explained that the data compiled for Ranexa showed that "the drug would never be approved." CW4
19 was concerned about certain studies that were included in the FDA package s/he helped prepare.
20 The results between studies were different, and if one study in particular (the Russian study) was
21 removed, the data would be unfavorable. CW4 spoke with individuals in CV Therapeutics' internal
22 regulatory department who admitted that "Ranexa would not be approved based on the current data."

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CV THERAPEUTICS (LEAD)

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