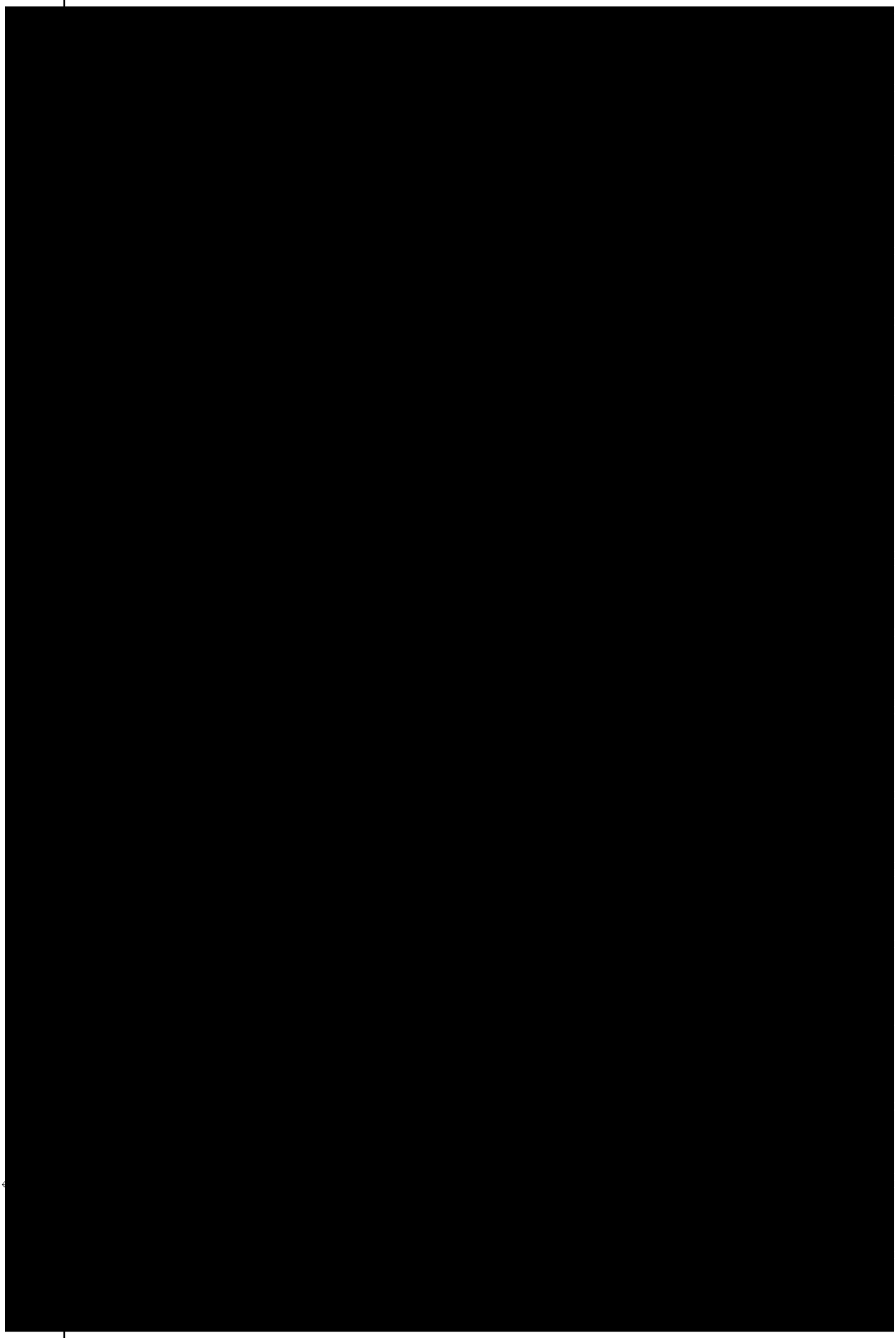
Risperdal in BPSD

The BPSD project shall be terminated as ethically, legally and quickly as possible. The team should prepare a DCC presentation in the implications of exit.

Risperdal in BPSD

Agenda

- Status of the project
- How we can terminate the program
- Ethical, regulatory and commercial implications
- Alternative proposal



Risperdal in BPSD - Regulatory status US

1Q99: FDA requests additional safety analysis for sNDA.

3Q99: Agreement with FDA to submit safety update once new controlled data available.

1-2Q00:
- FDA position : "Psychosis in Alzheimer's Disease" is valid diagnosis and claim; need 2 positive trials.
- USA-63 : accepted as positive trial, so 1 additional prospective positive study required.

  (Lilly/Astra will need 2 positive trials)

1Q01: FDAMA program accepted by FDA for RIS-USA-63 & 70

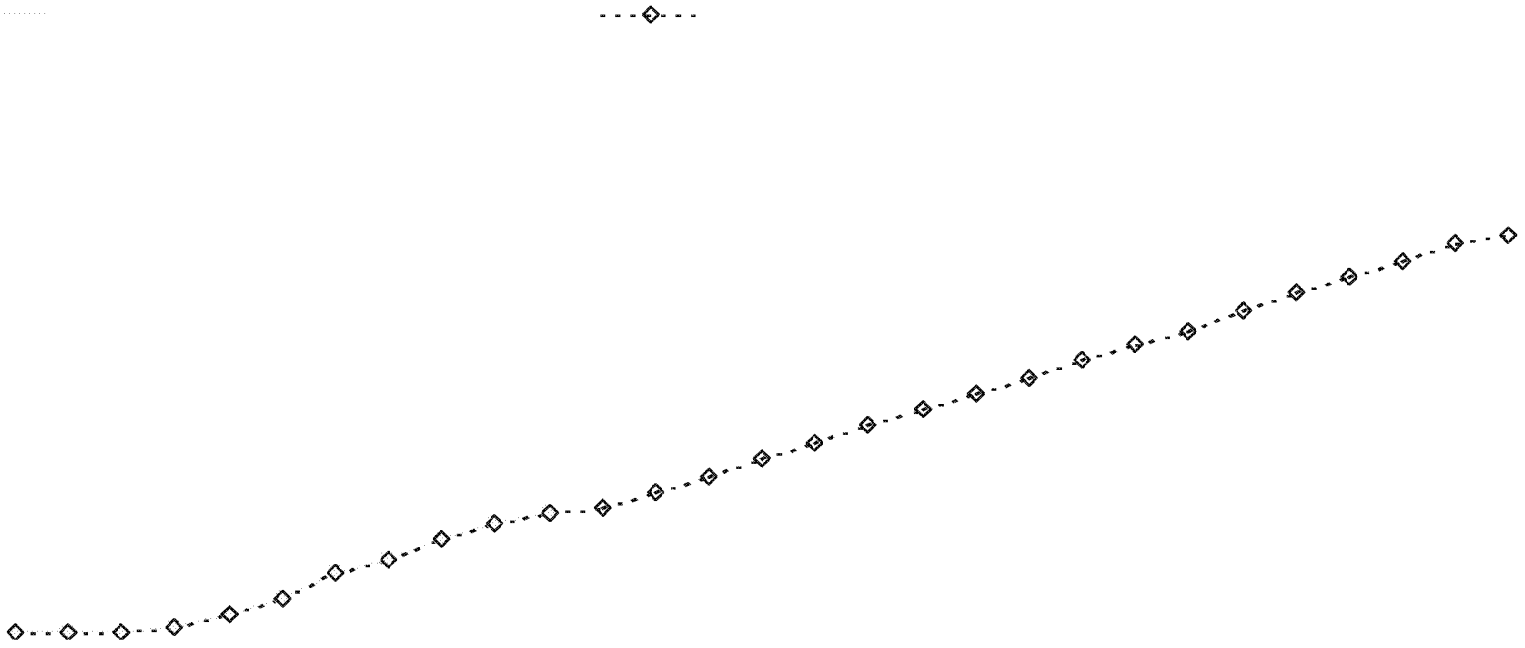
Aug 01: CVA document and proposed label change submitted to FDA

4Q01: Submission of safety update

Risperdal in BPSD - Present status of studies (Aug. 27)

	Active Sites	Pts Entered	Randomized	LPO	Filing
RIS-USA-63	-	-	462	Completed	-
RIS-USA-232	34	128	103 / 408	3 / 03	10 / 03
RIS-INT-83 (US + INT centers)	39	18	6 / 408	TBD	TBD

USA-232 Recruitment Rate



Risperdal in BPSD - How we can terminate the program

- Rationale towards investigators and medical community: "significant delays in recruitment and consequent approval"
- Included patients get final evaluation at next visit + provision for patients to be restabilized.
- Inform FDA and stop running FDAMA program (dissimination of publications RIS-USA-63 & 70)

Risperdal in BPSD - Financial savings ($MM)

	2001	2002	2003
RIS-USA-232	3.7	7.4	1.4
Spent + stopping costs	-2.4		
RIS-INT-83	4.0	7.5	1.5
Spent + stopping costs	-2.0		
Total savings ($ MM)	3.2	14.9	2.9

Risperdal in BPSD - Implications of Discontinuation

Ethical/Moral

- **Relinquish obligation to patients, caregivers & providers**
  - ➢ *Over one-half* of all antipsychotic-treated dementia patients are currently using Risperdal in US
  - ➢ [redacted]
  - ➢ Need to clarify significance of CVA signal
  - ➢ Concerns/misperceptions will be raised by Advocacy (NAMI & NMHA) and Opinion Leaders / Associations (IPA & NIMH), and healthcare providers

Risperdal in BPSD - Implications of Discontinuation

Regulatory

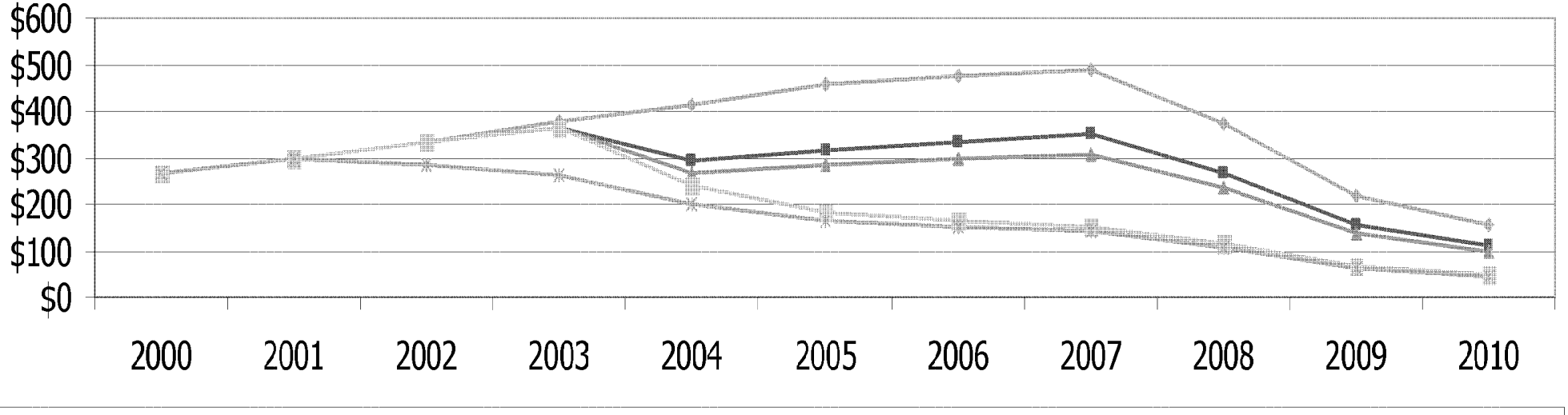
- **Credibility with FDA:** As the leader Janssen was 1st to file; prompted March Ad Board; led debate/discussion. Abrupt cancellation may be questioned.
- **Label at risk:** CVA observation remains unresolved with increased risk for unfavorable label that will impact entire brand.
- **FDAMA:** Must discontinue dissemination of USA-63 & 70 trials and may need to send 'Dear Prescriber' letter. FDAMA intentions may be questioned.
- Impact on EU/global (re)submission?

Risperdal in BPSD - Implications of Discontinuation

Commercial

- **Share loss will impact entire brand (not just dementia)**
  - Loss of ability to disseminate USA-63 & 70 data (competitive disadvantage)
  - Competition will mis-represent as a safety/efficacy 'concern'
  - Will initiate loss of formularly status and share
  - PCP opportunity is significantly compromised
- **Loss of Janssen strategic platform and goal to be #1 in ElderCare:**
  - Risperdal is the foundation of the J&J LTC portfolio
  - Will impact all Janssen growth brands: Risperdal (total), [redacted] (e.g., J&J contract leverage, ElderCare sales force justification, field retention, morale, etc.)
- **Trial enrollment/completion for Zyprexa, Seroquel and Abilitat will accelerate**

RISPERDAL DEMENTIA FORECAST COMPARISON
(US sales in millions)



Incremental Sales*:	$1.9B	$1.1B	$891MM	$230MM	-
NPV :	$475	$257	$197	$68	-

***Cumulative 2001-2010**

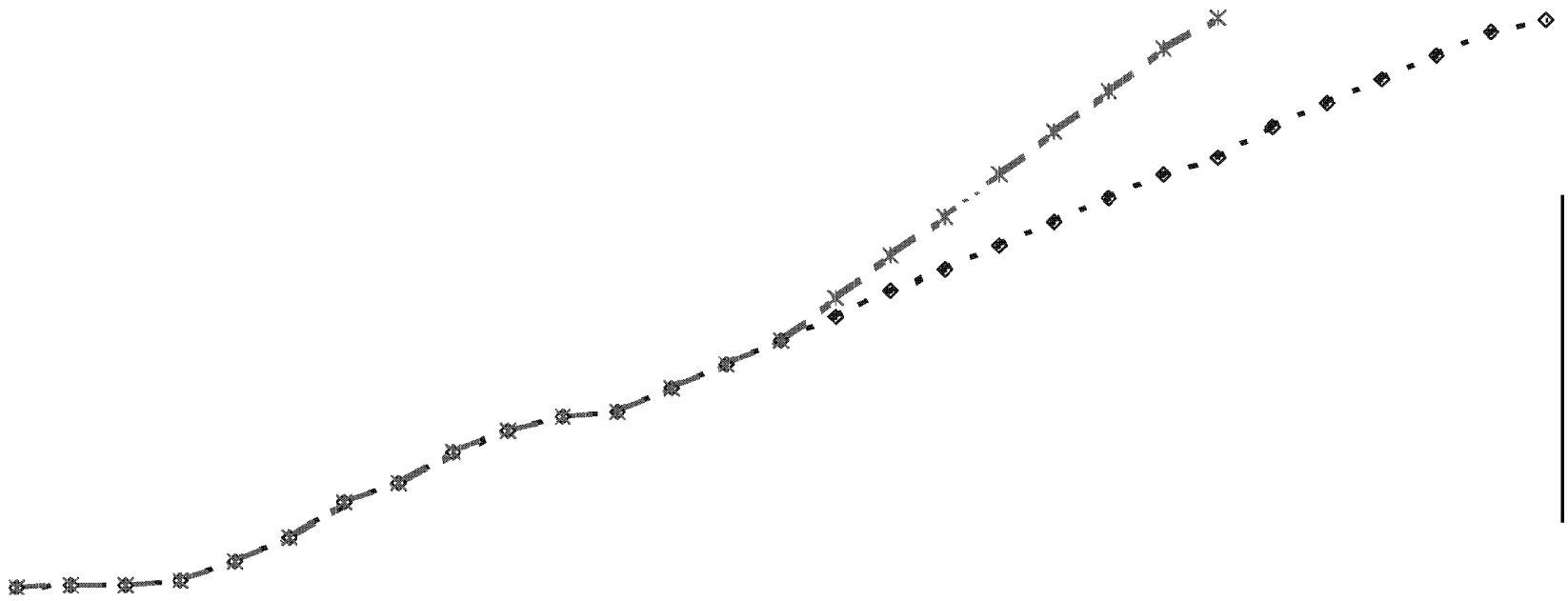
Risperdal in BPSD - Alternative proposal

- Continue RIS-USA-232 to obtain indication (at least to investigate the CVA signal)
- Stop RIS-INT-83 (too slow recruitment) and switch 10 best US sites to RIS-USA-232 => speed up RIS-USA-232
- File ≤ 10/03 if USA-232 is positive
- Savings: 2001 - $2.0MM
  2002 - $7.5MM
  2003 - $1.5MM
- $ 1.1 Billion incremental US Sales; $257 Million NPV*

* 1 year delay (2Q04 launch); 10 yr cumul. sales

BACK-UP

USA-232 Recruitment Rate



Current US Labeling

Identical 'Precautions' Section for CVA

PRECAUTIONS

General

Orthostatic Hypotension:

[Risperdal®/Zyprexa®/Geodon®] should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g....

Current US Label

Differences in CVA Labeling

Risperdal

ADVERSE REACTIONS *{nothing reported from registration trials}*

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causality) related to Risperdal® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated…

Zyprexa

ADVERSE REACTIONS *{as reported in registration trials}*

Cardiovascular System

Frequent: hypotension; *Infrequent*: bradycardia, cerebrovascular accident,….

Geodon

ADVERSE REACTIONS *{as reported in registration trials}*

Cardiovascular System

Frequent: hypertension; *Infrequent*: bradycardia, …; *Rare*: first degree AV block, cerebral infarct, cerebrovascular accident,…

Note: Infrequent = 1/100 - 1/1000; Rare = <1/1000

Proposed US Label Change for Risperdal

ADVERSE REACTIONS

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causality) related to Risperdal® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, cerebrovascular accident, diabetes mellitus aggravated…

Worst Case Label for CVA Data

FDA mandates CVA inclusion in the geriatric sections (PK, use, dosing) of the label along with a description of the risk factors found in the analysis

e.g. "...higher risk of CVA in elderly patients with advanced age and prior history of vascular disease..."

Worst Case Impact of CVA Data

- Other drugs with serious AE label changes still demonstrated growth:

- Potential effect on Risperdal difficult to estimate, but *unlikely* to have significant financial impact. (-2% = $5.3MM; -5% = $13.3 MM; -10% impact = $27MM)*

*** Based on dementia sales forecast of $276MM**