

**Therapeutic Class Review  
Olanzapine Heavyweight Team  
Agenda**

**Team Mission**

**Conclusions from Submission Package**

**Team Goals**

**Key Study Projects**

- **Study Specifications**

**Discussion**

**Conclusions**

ZY 2038 85

# **Two Aspects of the Heavyweight Team**

## **Team's Mission**

- 1. Expedite launch in two-thirds of the  
global major markets**
- 2. Optimize the early commercialization  
of the product**

# Goals

- **Execute, analyze, and write up a series of core registration studies designed to illustrate olanzapine's superior profile (safety, efficacy, functional well being, economics) to both**
  - (a) placebo and
  - (b) a representative conventional antipsychotic (haloperidol)

# Goals

- **Institute a “second wave” of clinical investigation (‘96, ‘97) for the following purposes:**
  - goal 1    optimize pricing decisions**
  - goal 2    prepare for timely launch in selected type II countries requiring local trials (free sales certificate driven)**
  - goal 3    differentiate product attributes of olanzapine from key competitors already in the marketplace**

# Goals

**goal 4** leverage the recent explosion of clinical and neuroscience activity in the schizophrenia to ideally position olanzapine as the innovator in psychosis management among our customers through publication

**goal 5** select and implement potential registrations quality trials among “new indications” section of the package insert capable of significantly growing the market potential/contributing knowledge in suspected areas of high “off-label” utilization

# Goals

- goal 6**      **recognizing local market idiosyncrasies,  
provide funding to engage key opinion  
leaders in publication worthy trials of  
interest**
  
- goal 7**      **cutting edge neuroscience or market-driven  
opportunities that will emerge during the  
planning cycle as “pilot” opportunities**

# Key Study Projects

Goal - which one or more are served by the proposed study?

Objective - desired results

Strategy - how it will be achieved

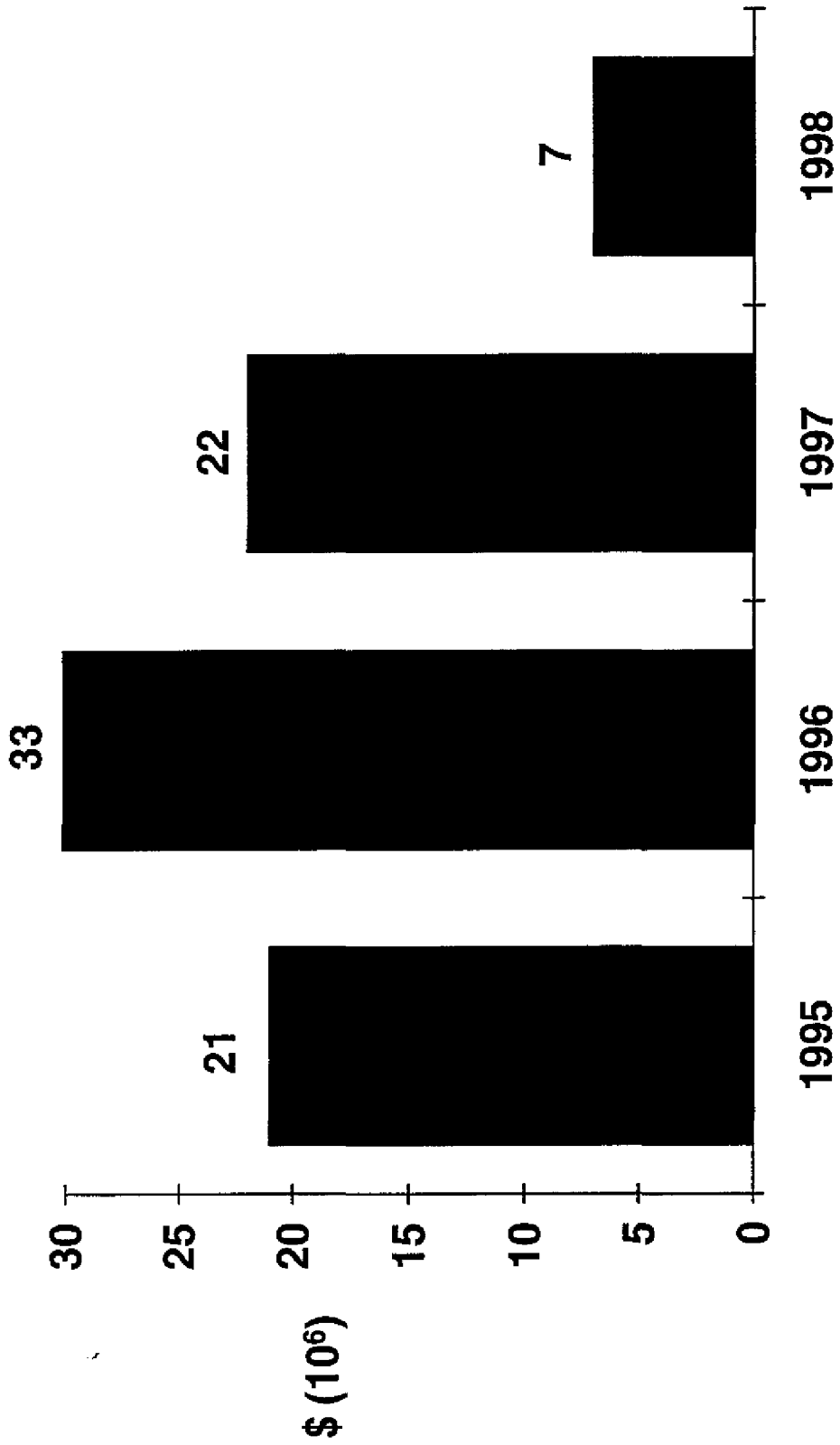
Task - necessary resources

	subjects
	countries
	comparator
	\$
	duration

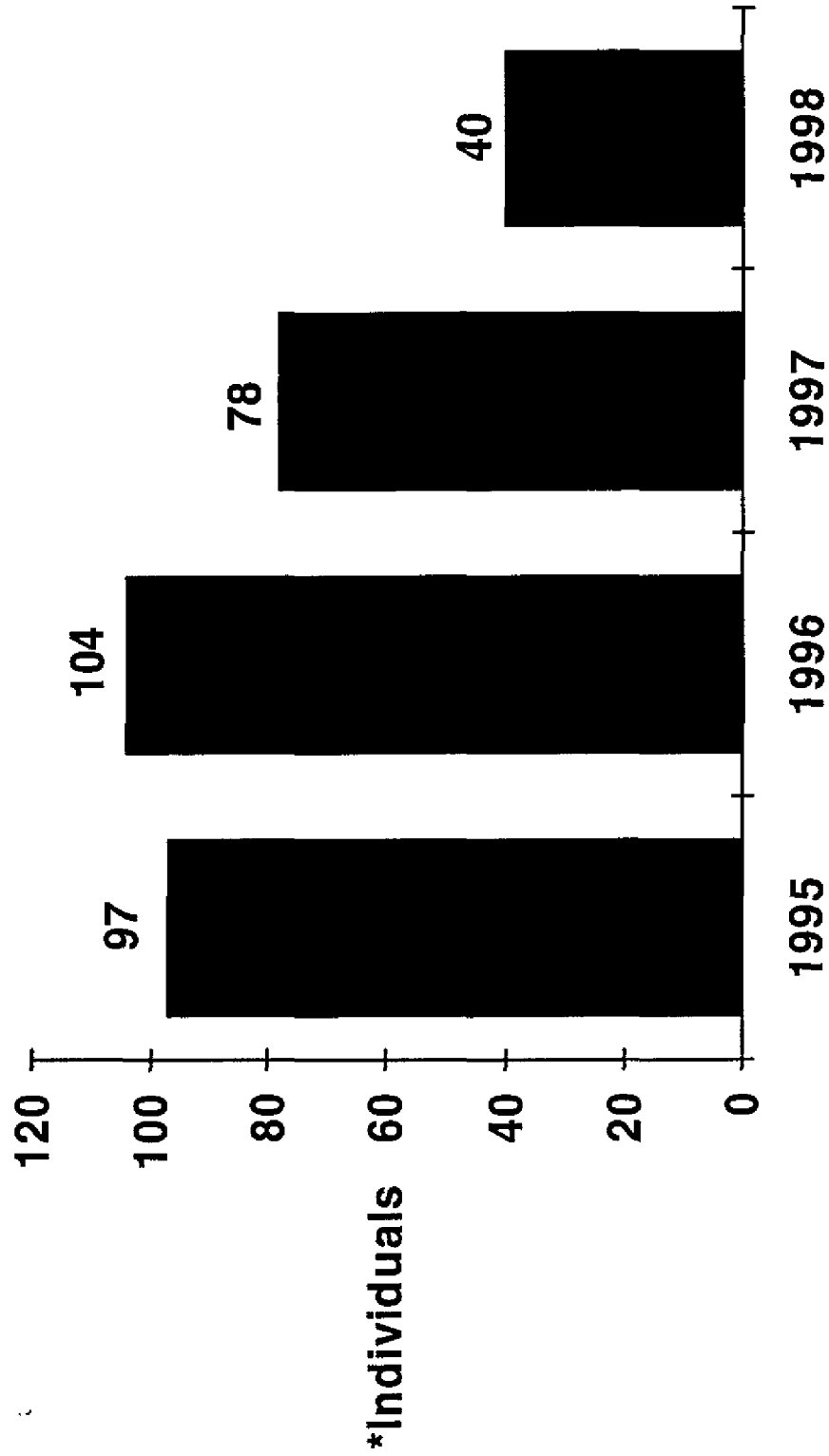
# 1996 Grants

<b>Continuing \$\$</b>	<b>18123</b>
<b>New \$\$</b>	<b><u>14953</u></b>
<b>Total \$\$ =</b>	<b>33076</b>

# Clinical Grants - \$

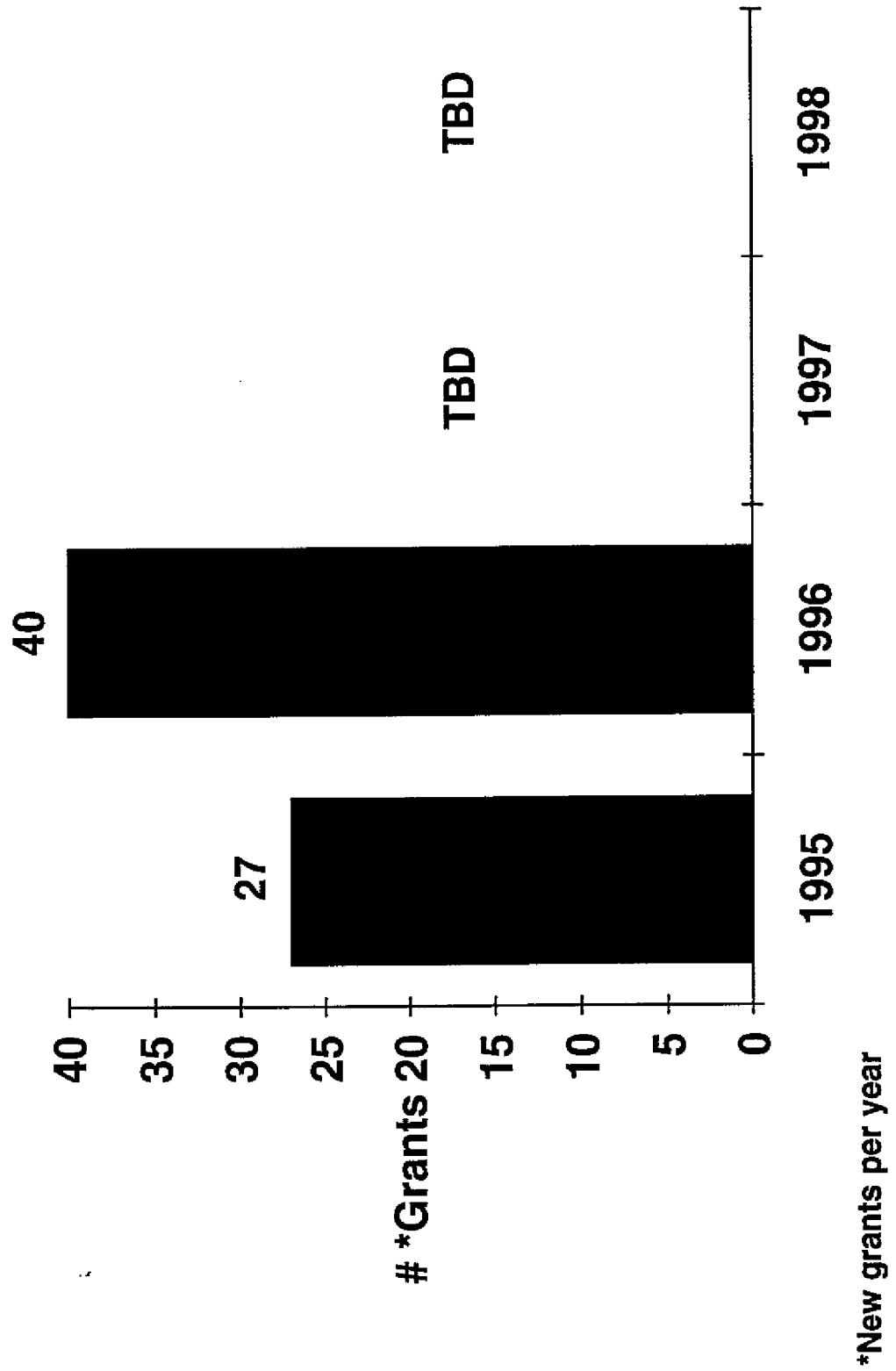


# Clinical Grants - Medical Plans and Data Management Headcount



\*Includes CRAs, CRPs, Systems, Statisticians, Secretaries, CIAs, CRP Secretaries, and Contractors

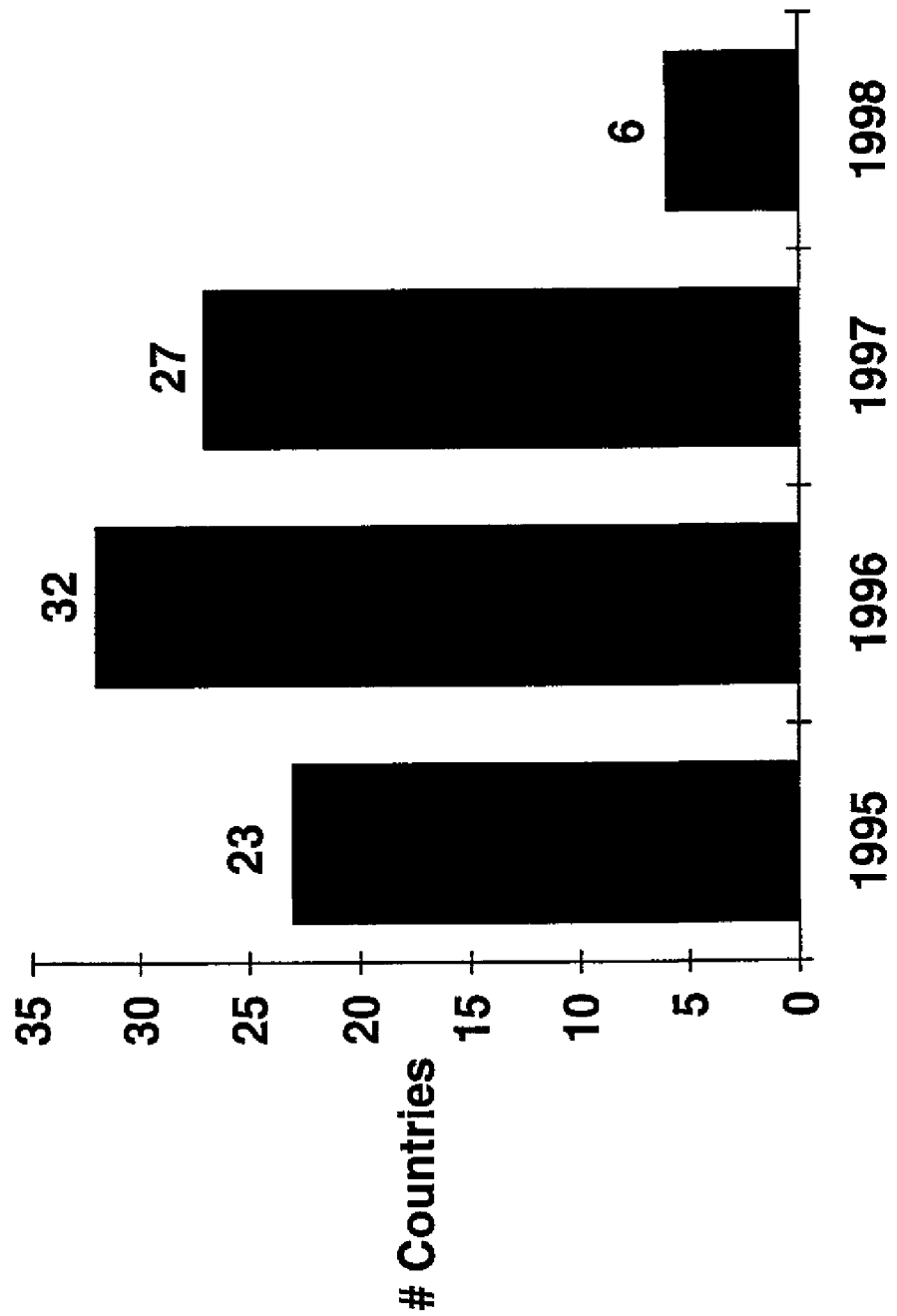
# Clinical Grants - Number



# Clinical Grants - Patient Enrollment

- add graph

# Clinical Grants - Countries Participating





# Hong Kong Registration - Professor Lieh-mak

Goals - 2, 3, 6

Objective - Olanzapine will be comparable or better than Haloperidol on efficacy and superior in it's safety profile among a Chinese cohort

Strategy - Double-blind comparator trial with the most influential opinion-leader in the region

Tasks -

- subjects N=60 (equal distribution)
- country (1) Hong Kong (China)
- comparator (Haloperidol)
- cost (\$000) \$330
- duration 6 weeks (3 month extension)

SIT 1 Aug  
Start 31 Oct 95  
Terminat

# Family Burden Questionnaire - Professor Maj

Goals - 1, 3, 6  
Objective - Eval. of a large # of schiz. pts with the family burden questionnaire and OLZ treatment eval. in relation to this FBQ scale.  
Strategy - A comparative study of OLZ pt's current tx with regard to caregiver burden/outcome. It will be leveraged for a comparative health economics argument with a key opinion leader.

- Tasks -
- subjects N=480
  - country (1) Italy
  - comparator (Haloperidol)
  - cost (\$000) \$300 (Corporate Contribution)
  - duration 6 months

*T. C. ...*

Tina + Nicole  
L. Liaw

ZY 2038 101

# Clozapine Comparator - Multistate Europe

Goals - 1, 3

Objective - Olanzapine will be equally/more efficacious than Clozapine and with a better safety profile

Strategy - Clozapine is viewed as the "gold standard atypical" but with numerous safety liabilities; a superior olanzapine risk:benefit profile would permit positioning as a "first-line" therapy and facilitate regional pricing

Tasks -

- subjects N=220 (equal distribution)
- countries UK, SPN, FRA, GER, IT, NOR, SWE, NETH, SA
- comparator (Clozapine)
- cost (\$000) \$1500
- duration 8 weeks (ext. 24 weeks)

??

RMC

# Late-Onset (Geriatric) Schizophrenia - Multistate Europe

Goals - 3, 4, 5, 6

Objectives - Olanzapine will prove to have a superior therapeutic profile in this special population

Strategy - Late onset psychosis has recently been proposed to differentiate on the basis of clinical phenomenology/very few treatment studies have been conducted in this population.

Characterizing and contrasting across our database will be of scientific interest/data should permit further package insert changes/data should expand commercialization

Tasks -

- subjects N=110 (equal distribution)
- countries GER, SPN, UK, IT *only 2 countries now*
- comparator (Haloperidol)/=DB
- cost (\$000) \$231
- duration 6 weeks (open label extension)

*Not RMC*

June 1996  
Oct 1 1996  
Stacy

# Psychotic Comorbidity In Alzheimer's - Global

Goals - 3, 4, 5, 6

Objectives - Olanzapine has equal or better efficacy and superior safety to the most commonly used comparator and placebo in this patient group

Strategy - Through the use of a DB placebo and comparator controlled design olanzapine can be positioned for this new indication in a very large clinical population (commercialization) through a single protocol, 2 trial study employing novel rating instruments and surrogate measures; a superior profile will clearly differentiate us from competitors

- Tasks -
- subjects N=450 (equal distribution)
  - countries US, UK, CA
  - comparator (placebo; Haloperidol)
  - cost (\$000) \$2,700
  - duration 10 weeks (16 week blinded extension)

1- Q2 96  
2- G3

# Mania of Bipolar Disorder - Global

Goals - 3, 4, 5, 6

Objectives - To demonstrate olanzapine is superior to both placebo and lithium in the acute control of mania and superior to placebo/equivalent or equal to lithium in relapse prevention

Strategy - While moderately effective in relapse prevention, the side effect profile of lithium and limited anti-psychotic efficacy limit its use. Two positive-controlled trials would enable registration for a major new indication, as well as, provide comparative information versus lithium for publication. Such a claim will help differentiate from risperidone.

- Tasks -
- subjects N=450 (equal distribution)
  - countries US, CA, FR, GER, NETH
  - comparator placebo/lithium
  - cost (\$000) \$4500
  - duration 6 weeks acute (46 week DB maintenance)

# Neuroimaging Bundle - Global

Goals - 3, 4, 6

Objectives - The receptor occupancy profile of olanzapine will be shown to be unique and theoretically linked to product attributes

Strategy - Utilize the latest neuroimaging techniques, in the hands of key opinion leaders, to show comparative data from:

- in vivo pharmacology - PET
- regional blood flow - SPET/MRI
- regional energy - SPET/MRI
- regional metabolism - functional MRI
- clinical correlations - all

to maximally leverage publications in this accelerating field of interest

- Tasks -
- subjects N=134 ; # studies = 8; OL & DB
  - countries US, CA, SWE, UK, GER, SP, IT
  - comparator variable (ex. HAL, CLOZ, RISP)
  - cost (\$000) \$943 (bundle)
  - duration range single dose to 6 weeks

*Template*

# 1994 Templates - Continuation Multistate

Goals - 6, (1, 2, 4)

Objectives - To provide local olanzapine experience in research areas of mutual interest with corporate retention of core safety only

Strategy - Individual affiliates identify key influencers in their market and applicable research proposals which are subject to peer review. Prioritized studies must demonstrate commercial and/or registration value with a high probability for publication

- Tasks -
- subjects            variable (total N=250)
  - countries           AUSTRAL, GER, IT, AUS, MEX
  - comparator        range OL to blinded CLOZ, RISP, and HAL
  - cost                    1996 carryover = \$1822
  - duration             range 4 weeks - 22 weeks

# 1995 Templates - Continuation

## Multistate

Goals - 6, (1, 2, 4)

Objectives - To provide local olanzapine experience in research areas of mutual interest with corporate retention of core safety only

Strategy - Individual affiliates identify key influencers in their market and applicable research proposals which are subject to peer review. Prioritized studies must demonstrate commercial and/or registration value with a high probability for publication

Tasks -

- subjects variable (total N=435)
- countries GER, NETH, MEX, US, BELG, SP, E. EUR
- comparator OL to blinded CLOZ, RISP, HAL, and FLU
- cost 1996 carryover \$2852; 1997 carryover \$290
- duration 4 - 20 weeks (OL ext.)

# Negative Symptom Study - U. S.

Goals - 3, 4, 5

Objectives - Demonstrate that olanzapine is superior to Haloperidol in predominant negative symptom patients with a clear safety advantage

Strategy - Olanzapine will be directly compared with Haloperidol in a sample of negative symptom patients to illustrate its effect upon primary negative symptoms and corroborate its atypical profile. Data should serve to strengthen package insert and publication on the emerging data linking negative symptoms and cognitive problems

- Tasks -
- subjects N=300
  - countries US
  - comparator several doses of HAL
  - cost (\$000) \$6,000
  - duration 12 weeks (12 week blinded extension)

Study 16

Handwritten notes: "Lan", "10/16/09", "PMD", "Q3", "CEN"

# Relapse Prevention - U. S.

Goals - 3, 4, 5

Objectives - To show the superiority of olanzapine (10 - 20 mg) to either a therapeutic dose of a standard comparator or a subtherapeutic dose olanzapine ( $\leq 2.5$  mg)

Strategy - Implementation of a FDA advised design to seek package insert change to include "relapse prevention" which would differentiate olanzapine from others and provide publication support for the emerging concept of schizophrenia as a chronic, recurrent disease

- Tasks -
- subjects 200
  - countries US
  - comparator Haloperidol
  - cost (\$000) \$1,500
  - duration 52 weeks

Handwritten signature: "G. J."

# First Episode Schizophrenia - U. S./Netherlands

15 Jan 96  
15 June 96

## Goals -

3, 4, 5

## Objectives -

Provide evidence that olanzapine is a superior treatment in this cohort for prevention of disease-associated progression

## Strategy -

Within an enriched sample evidence suggests an atypical might slow or prevent progression of a number of disease features; working with the leading researcher in this area the study should serve to modify labeling, further differentiate the product, and publish "cutting-edge" data

## Tasks -

- subjects
- countries
- comparator
- cost (\$000)
- duration

N=232 — 130  
 US, NETH  
 Haloperidol  
 \$12,250  
 1 year (optional ext per year)

4 5/14/96  
15 June 96

# Refractory Patients - U. S.

Goals - 3, 4, 5

Objectives - Evidence that olanzapine has superior efficacy in the treatment of schizophrenic patients resistant to a "typical" neuroleptic

Strategy - This will serve as a second registration study (assumes first study is positive at interim) replicating the classical work of Kane, et al with clozapine. Open label non-responders to chlorpromazine will be blindly randomized to continued CPZ or OLZ; it is expected OLZ will clearly differentiate with its product profile.

- Tasks -
- subjects N=50
  - countries US
  - comparator Chlorpromazine
  - cost (\$000) \$375
  - duration OL 4 weeks and DB 8 weeks (12 weeks ext.)

Oct 98 / Jan 99

# Naturalistic - U. S.

Goals - 1, 3, 6

Objectives - Provide data on olanzapine outcomes in a less controlled setting approximating "real-care" scenario versus conventional agent(s)

Strategy - Utilize a research method similar to the current group health Redacted design with a key, prepaid Lilly customer to ensure competitive outcome data to maximize pricing in a HMO setting (versus standard treatments)

- Tasks -
- subjects N= 500
  - country US
  - comparator TBD (blinded)
  - cost (\$000) \$1,500
  - duration 24 weeks

*PCS reviewed 9/6  
Z-01*

*1/20/17  
96400/1  
L1 1271*

# Disease State Management - U. S.

Goals - 3, 5

Objectives - Validate a treatment algorithm/patient monitoring system

Strategy - Explore a candidate DSM strategy versus no intervention and document an improved outcome to expand the use of olanzapine

- Tasks -
- subjects 80
  - countries US
  - comparator no DSM intervention
  - cost (\$000) \$560
  - duration 24 weeks

Oct 95 / Jan 96

Team

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# Comorbidity - Alcohol - Global

(12/15/15)  
9/16/15  
9/16/15

Goals - 3, 4, 5

Objectives - Olanzapine is safe within a dual disordered population and effective in improving both 1° psychosis and 2° patterns of abuse. This profile would exceed that of a comparator.

Strategy - Substance abuse is a frequent complication in the management of psychosis. It is believed that an effective intervention with the 1° psychosis (coupled with the 5-HT profile of olanzapine) will benefit 2° abuse. Such a demonstration would be contemporary with current clinical concerns and highlight product differentiation potentially useful in labeling.

- Tasks -
- subjects N=60
  - countries US (Sweden and Denmark?)
  - comparator Haloperidol
  - cost (\$000) \$1,000
  - duration 24 weeks

# Pilot Studies - Global

Goals - 4, 6, 7

Objectives - Innovative neuroscience pilots to better leverage olanzapine in future

Strategy - Quick response time to peer reviewed submissions from global preclinical and clinical leaders. these highly “cutting edge” projects will provide substantial publication/presentation material to energize scientific and medical customers

- Tasks -
- subjects variable
  - countries global
  - comparator variable
  - cost maximum \$50,000 per grant
  - duration variable, but target for quick turn around

# Plan D Studies - Global

Goals - 3, 4, 5, 6, 7

Objectives - Implement timely marketplace-driven protocols to better commercialize olanzapine

Strategy - Recognizing the dynamics of the marketplace, this is a strategy to have a cross-functional review group identify contemporary issues and implement studies to better differentiate, establish, and support the product in the literature, labeling, and opinion leaders' mind set.

- Tasks -
- subjects variable
  - countries global
  - comparator variable
  - cost variable
  - duration variable

# Line Extensions - Global

Goals - 1, 3, 5

Objectives - Consistent with the Life Plan, offer customers highly desirable product presentations to promote broader use/better outcomes.

Strategy - A thorough analysis of market research has generated a list of options which will be prioritized and cross-referenced to dimensions of technical feasibility/NPV. Then appropriate registration activities will be initiated leading to eventual line extensions that differentiate us from competitors and optimize commercial returns.

Tasks -

- subjects
- countries
- comparator
- cost
- duration

TBD