LAO Aripiprazole OW

Long Acting Oral aripiprazole Once Weekly

An alternative option to Long Acting Injectables (LAI) in the rapidly expanding market for prevention of psychotic relapse

Zysis

Management Team

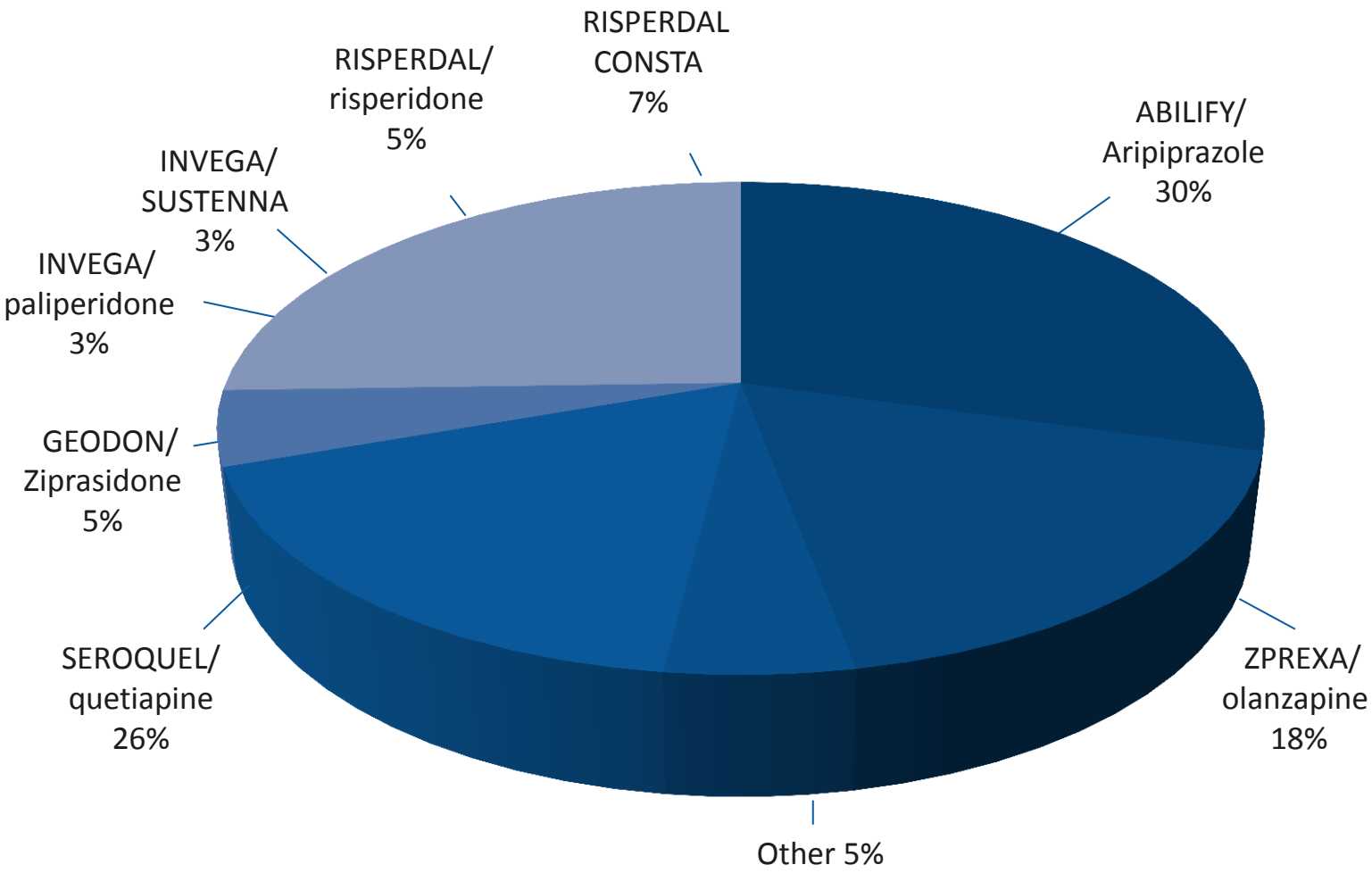
- Dr Peter Cozens, Non-Exec Chairman
  - More than 30 years' experience in licensing
  - Chairman of the Intellectual Property Advisory Committee of the UK BIA
- Dr Ian Wilding, VP – Development
  - Founder of Pharmaceutical Profiles, a Phase 1 CRO
  - Leading authority in drug delivery and formulation development, with 250 patents and publications
  - Advisor to US FDA
- Mr Russ Pendleton, VP – Commercial
  - 14 years in big pharma Sales & Marketing, including the global launch of three psychiatric drugs – Global Brand Manager – Seroquel, AZ
  - Founder of Perimeter Communications Medical Conference company; 15 years of establishing and managing conferences in psychiatry and neurology

Preventing Relapse in Schizophrenia and Bipolar Disorders with oral once-weekly, monitored/supervised therapy

Opportunity Summary

- Our Long Acting Oral aripiprazole Once Weekly product **with monitored/ supervised dosing** is intended to reduce relapse rate.
- Target Patient Population = “moderate” maintenance population of schizophrenia/ psychotic patients.
  - These patients require approaches to increase adherence but are not ready yet for the highly invasive and extremely expensive option of the long acting injectable (LAI).
- This is a low-risk project with a high probability of technical success given the now established pharmacokinetic (brain & plasma), safety and efficacy profile of aripiprazole in schizophrenia.
- Fast & inexpensive clinical plan with anticipated US approval in 2018
- Zysis forecasts peak year sales of circa 900 million USD.

Prior to patent expiry aripiprazole was the market leader in the world wide Atypical Antipsychotic Market



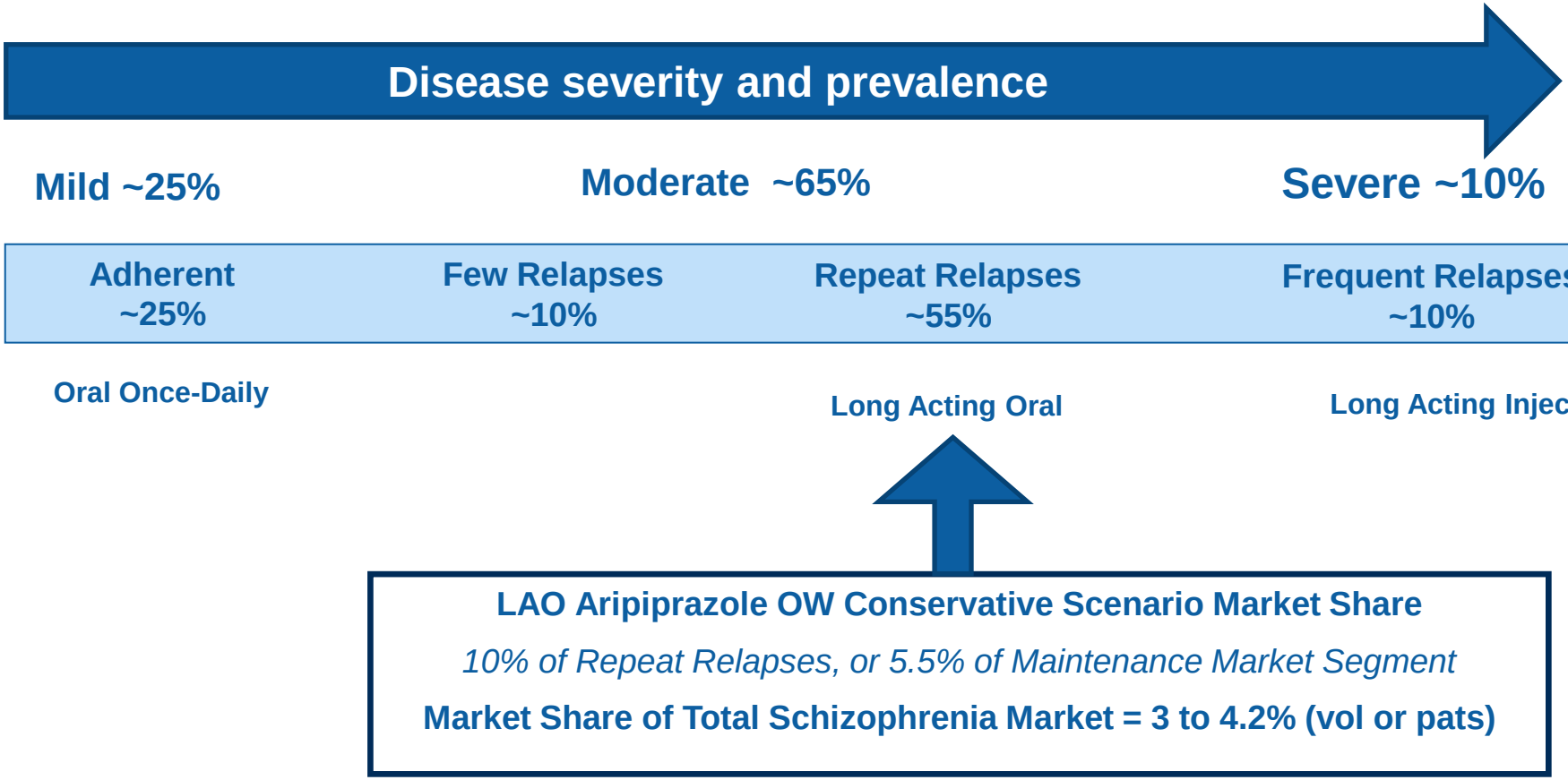
Targeting unmet needs in schizophrenia – non-adherence

Zysis is developing a true aripiprazole OW oral formulation

- Non-adherence rates are extremely high with schizophrenia therapy
  - ~75% of patients with schizophrenia are non-adherent within 2 years of being discharged from hospital[1]
- The consequences of non-adherence are medically (and economically) severe
  - 69% of patients with poor adherence suffer a relapse[2]
  - (Only 18% of patients with good adherence suffer a relapse[2])
- Poor adherence is a predictor of poorer outcomes
  - Poorly adherent patients are hospitalised **more often**, and for **longer periods of time**[3,4]

References
1. Weiden PJ et al. Psychiatr Serv, 1995; 46: 1049–1054
2. Morken G et al. BMC Psychiatry, 2008; 8: 32–38
3. Valenstein M et al. Med Care, 2002; 40: 630–639
4. Gilmer TP et al. Am J Psych, 2004; 161: 692–699

LAO Aripiprazole OW – Market Share Analysis
Maintenance Market Segment*



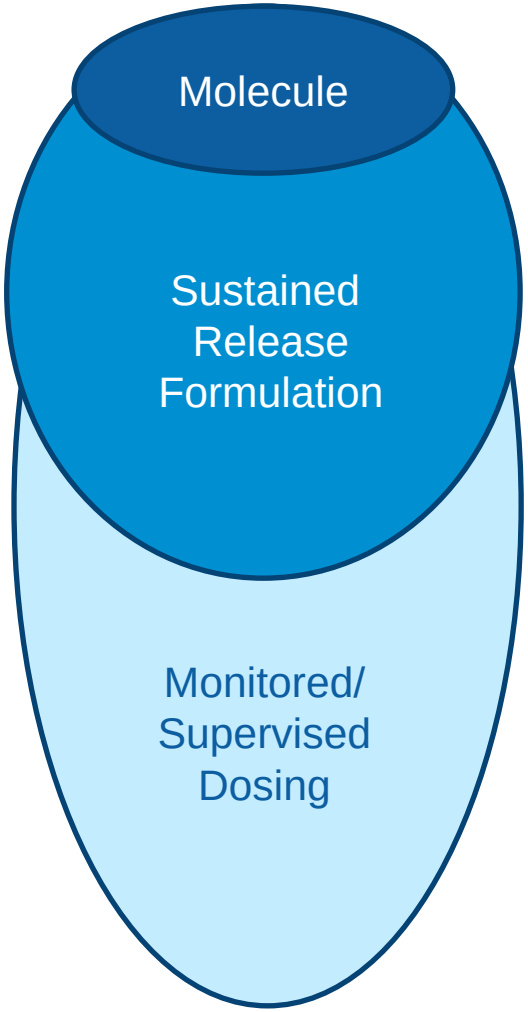
*Maintenance Market Segment represents 70% of total schizophrenia market

LAOs – An Alternative to LAIs for Psychotic Relapse Prevention

LAO Aripiprazole – With Monitored/Supervised Dosing once weekly - targets and prevents relapse before resorting to LAI therapy

- **First-in-class** antipsychotic therapy for orally dosed relapse prevention
- **Better outcomes** for doctors & patients – fewer relapses
- **Direct cost savings** for payers - reducing relapse & medical staff costs
- **An earlier** and more cost effective **alternative** to LAIs

LAO Aripiprazole OW – Targeting Psychotic Relapse



The antipsychotic Aripiprazole has the best efficacy/side effect profile of all the atypicals

Our patent protected sustained release formulation allows for oral once weekly dosing to become a reality by increasing drug residence time at the site of action.

Monitored/ Supervised dosing ensures patients take every dose without forgetting and still demonstrates cost effective, health economic superiority to all other therapies.

LAIs Administered in Three Distinct Treatment Settings

LAOs can sit alongside this posology structure

Community Mental Health Centers

- Pivotal hub that connects to hospital and home
- LAI injection/ administration or home services

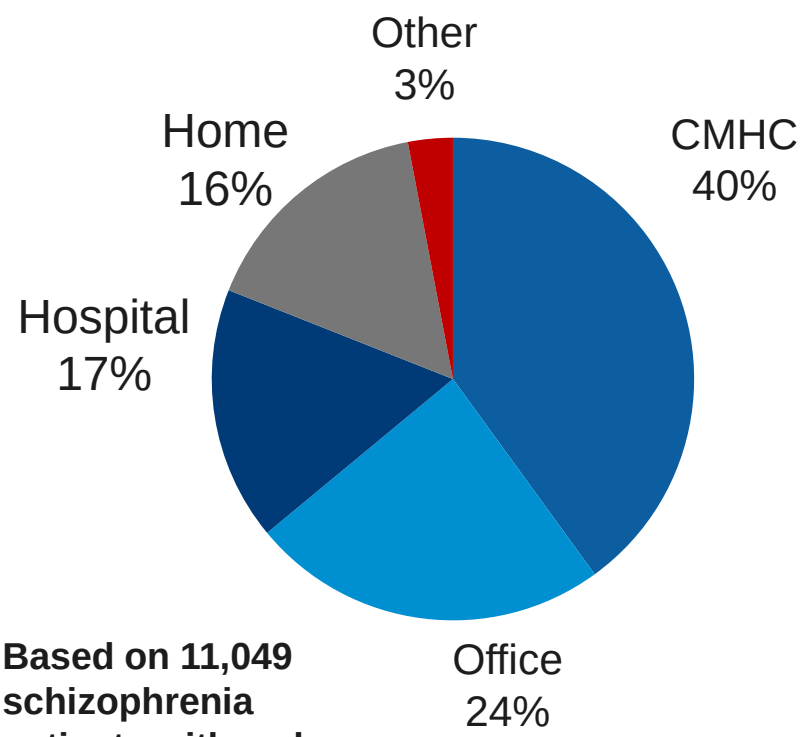
Private Offices

- Psychiatrists, supported by HCPs (nurses)
- May also treat other CNS disorders

Hospitals

- Short-term ER/inpatient services, with first LAI injection
- Connects patients with CMHC or private office for continued treatment
- Outpatient injection services

Treatment Settings for Administration of LAIs in Medicaid Patient Population



Based on 11,049 schizophrenia patients with a place of service associated with an LAI claim

“Monitored/Supervised” dosing of LAO aripiprazole OW

All the structures used for LAIs

- Using prior precedent of supervised dosing of LAIs by a variety of medical team staff in a several treatment settings (community mental health centers, hospitals, private offices).

+

Community Psychiatric Nurses

- Office lead but potential for community managed monitoring by visiting Psychiatric Nursing Staff

+

Case management personnel

- Additional case management personnel eg counsellors reporting back to senior medical team

Support Structures

- Electronic reminder/ monitoring systems help
- Allows ownership of relapse space
- Connects patients with care provision for continued treatment

Monitored/Supervised Dosing eradicates all potential issues that may arise with a OW Oral product

Issue

- Once Weekly dosing can be more difficult to remember than once daily dosing

Solution

- Monitored/supervised dosing takes away the responsibility of remembering from patients ensuring continuous therapy provision (in common with LAIs)

Issue

- Many psychotic patients are on several once daily medications.

Solution

- Monitored/supervised dosing ensures that at least the most important therapy (the anti-psychotic) is taken and reduces the number of drugs the patient has to remember to take OD.

Issue

- A OW product is simply a convenience product with no real therapeutic benefit so price has to be at generic level

Solution

- Monitored/supervised dosing ensures Relapse Rate Improvement which on a pharmaco-economic basis justifies a higher price than generics albeit much more cost effective than LAIs.

Launch Product Profile for LAO Aripiprazole OW

Feature	Benefit
Long acting oral – otherwise as effective/safe etc as the once daily oral	Patients only have to take their medicine orally, once weekly
Structures are in place to support monitored/ supervised patient dosing in the clinic & by medical staff/others in the community	The responsibility of remembering to take the treatment is taken out of the patients hands using existing care platforms
Observing the patient take the therapy can be done in the clinic by a minimally-trained person	Requirements to monitor dosing are not onerous – no litigation requirement for two in surgery cost, shorter paper trail, no needle disposal cost, no secure storage cost, no refrigeration cost, no waiting in surgery after dosing…all easier than a LAI
One year study shows relapse rate reduction *eg. from 45% to 20% for monitored/supervised once weekly dosing*	Patients stay out of hospital and symptoms are under control
HE modelling demonstrates substantial direct & indirect HE benefit priced at USD9 per day	Patients on oral OW therapy cost less overall, long-term to treat

USD 9 is justified by modelling and data generated through relapse rate improvement pricing study

Pricing and cost-effectiveness

Key concepts to build a strong cost-effectiveness argument

The argument justifying the price of LAO Aripiprazole OW:

- Risperdal depot achieved 17% relapse rate in a similar open label extension phase study
- LAO Aripiprazole OW should achieve at least an equal relapse rate to Risperdal Depot
- Targeted relapse prevention study undertaken in parallel with NDA review to verify relapse rate improvement and generate the data for LAO Aripiprazole OW pricing

Precedent is set with payers - LAIs use improvement in relapse rate to justify premium pricing

Modelling Monitored/Supervised Dosing for Aripiprazole OW

Cost benefits are achievable with medically supervised dosing over all other therapies

Cost Savings Per Patient Per year	USD
LAO Aripiprazole OW with medically supervised dosing at 9 USD/day	
Long-acting injectable Aripiprazole once monthly	***$5,899***
Long-acting injectable Paliperidone once monthly	***$4,804***
Long-acting injectable Risperidone twice monthly	***$4,648***
Long-acting injectable Generic once monthly	***$889***
Immediate release oral Branded daily therapy	***$3,712***
Immediate release oral Generic daily therapy	***$427***

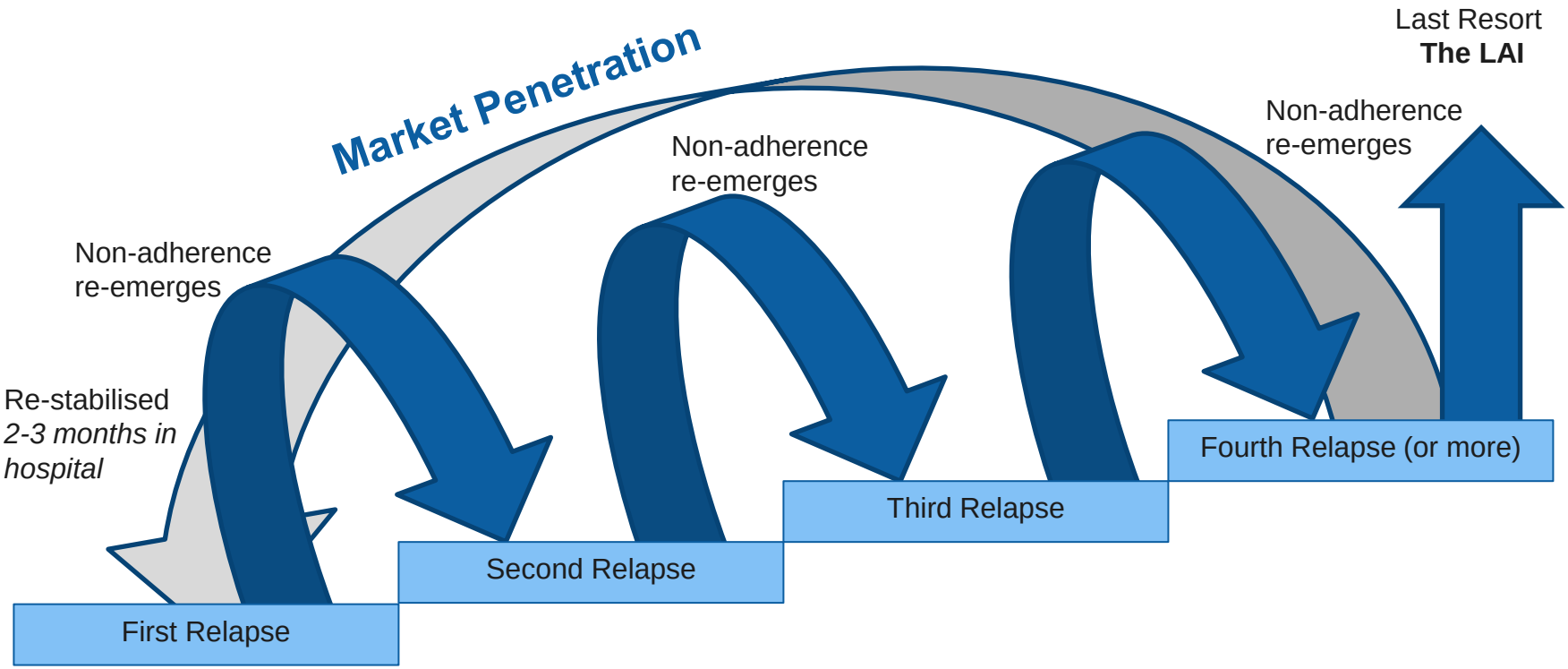
The costs of Schizophrenia therapy are driven by the cost of relapse

A treatment that improves relapse rates can justify a higher price (cf LAI Aripiprazole OM)

Upside Sales Analysis

Once the Monitored/Supervised strategy has achieved market acceptance…

Why wait for multiple relapses?



'To be used just before LAIs' *Becomes* 'To be used after first relapse, as non-adherence is clearly now an issue'

How can we scientifically achieve aripiprazole oral OW?

Three key characteristics define the strategy : -

Gastrointestinal compartment
Sustained release (5hr) formulation to control Cmax at higher doses

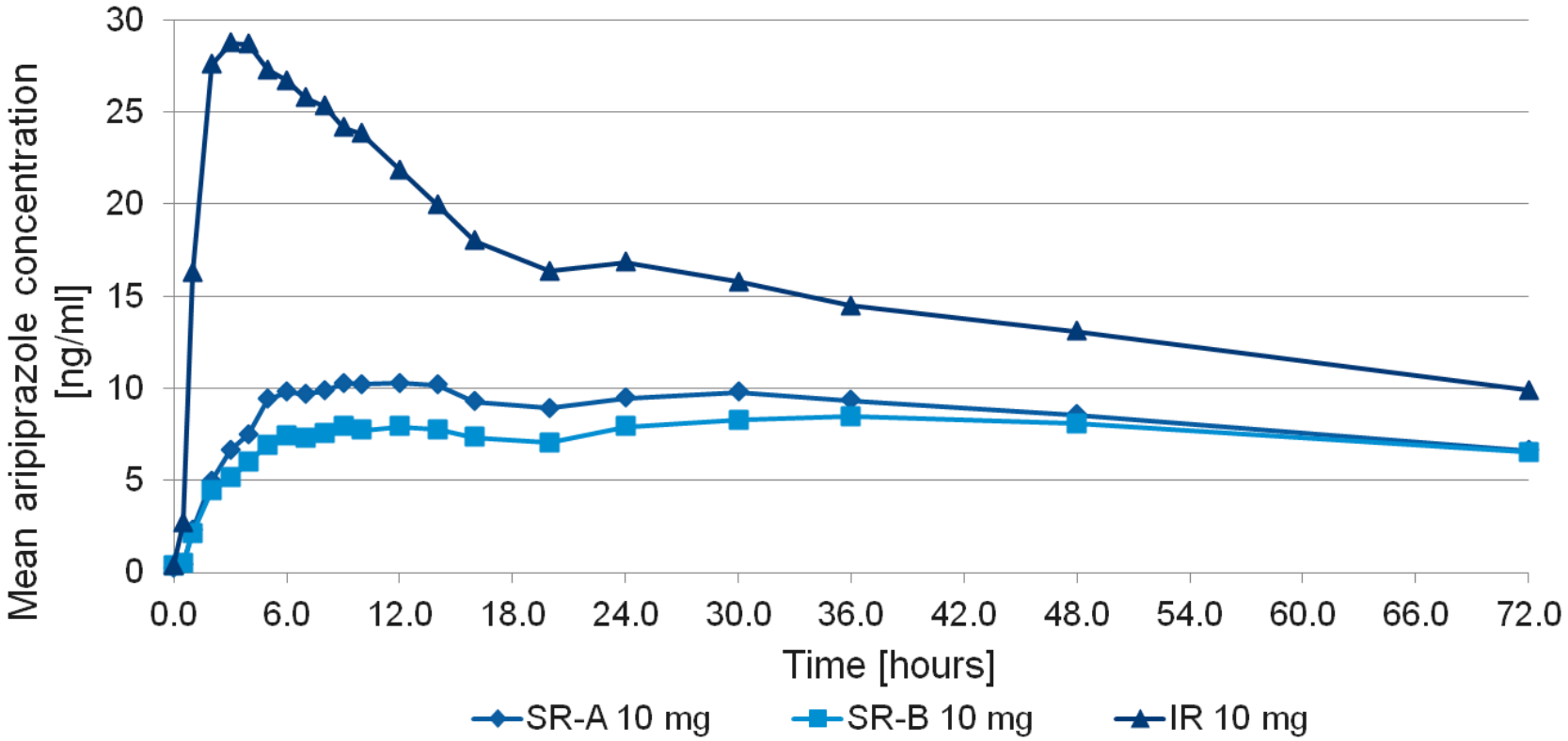
Plasma compartment
Long plasma aripiprazole half-life (3 days)

Brain compartment
Very slow aripiprazole dissociation from the D2/D3 receptors in the striatum

PK feasibility testing of early aripiprazole oral OW SR prototypes

Clinical evaluation of SR prototypes with 8 and 16hr in vitro release rates vs IR reference in 12 healthy volunteers

Extended absorption throughout small and large intestine but evidence of dissolution dependent bioavailability in the colon even at low drug doses



Zysis US Clinical and regulatory strategy for LAO aripiprazole OW

pk dose ranging study for aripiprazole OW in schizophrenic patients

Step 1

- Reformulate the initial prototypes using the same SR platform (ie HPMC matrices) to deliver entire drug dose in 4 to 5 hours (before colon arrival) which will allow for delivery of OW drug dose with dampened Cmax but with reduced risk of pharmacokinetic variability on dose escalation.

Step 2

- Pk Dose ranging, placebo-controlled multiple group clinical study in 45 schizophrenia patients (as defined by the DSM-IV-TR criteria)
- The primary objective of the study is to determine which dose of aripiprazole OW provides for therapeutically relevant plasma concentrations of aripiprazole with a plasma pharmacokinetic profile that supports once-weekly dosing.
- All patients will be randomized to receive either 70mg, 105mg or 140mg aripiprazole OW (n=15 per group (n=12 active/n=3 placebo)) on six occasions.
- Measurements will include blood sampling for pk characterisation on week 1 and 6 follow OW therapy and PANSS assessment.

Zysis clinical and regulatory strategy for LAO aripiprazole OW

Guidance for Industry : Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998) Section II. C.1.d.

"Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form"

Zysis will argue that the pk/pd relationship is well defined for aripiprazole avoiding the need for further efficacy studies but some clinical studies will still be necessary to support the pricing arguments around relapse prevention.

Zysis clinical and regulatory strategy for LAO aripiprazole OW

Relapse prevention study for pricing purposes

- “Head to head” comparison of aripiprazole oral OW vs generic once daily anti-psychotic
- One year study in 160 patients with schizophrenia or schizoaffective disorder (n=80 per group)
- Primary outcome measures: re-hospitalization rate at 3 months, 6 months and 12 months

Zysis IP position

Aripiprazole oral OW has a strong intellectual property position

- Zysis filed a UK patent application on the SR aripiprazole formulation, which includes the OW positioning, with a priority date of 26 September 2006.
  - A Patent Cooperation Treaty (PCT) application was filed 12 months later.
- Granted patent with broad claims in :-
  - US (November 2013)
  - Israel (August 2012)
  - Australia (August 2013)
- Divisional patent filed in the US in November 2013

Relapse Prevention in Schizophrenia and Bipolar Disorders with oral once-weekly, medically-supervised therapy

Summary

- A commercially differentiated opportunity targeting the clinical unmet need of adherence in the treatment of schizophrenia and bipolar disease
- A low-risk project with high potential returns
  - Good probability of technical success
  - Fast and inexpensive clinical plan
  - Forecasted peak sales of *circa* 900 million USD
- Anticipated US approval 2018
- Excellent IP Position in the US