

Aripiprazole Oral Once-Weekly

Addressing poor outcomes in the treatment of schizophrenia through the development of a once-weekly oral tablet

Zysis[®]

Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

Appendix



Improving treatment outcomes in schizophrenia

Zysis is developing a true aripiprazole once-weekly (OW) oral formulation

Summary

- The total market that an oral, once-weekly, patent-protected formulation of aripiprazole can target is 13.4 billion USD; Zysis forecasts a 5.5% market share by value, creating peak year sales of 600 million to 1 billion USD (70% US, 15% EU, 15% RoW)
- An FDA New Drug Application submission is anticipated within 3 years, with a total investment of only 23 million USD for clinical trial work required to reach this point
- This is a low-risk project; although it would become a novel, unique therapy in the antipsychotic market – a once-weekly oral – it is still a reformulation and, as such, has a >75% chance of achieving approval



Improving treatment outcomes in schizophrenia

Zysis is developing a true aripiprazole OW oral formulation

Targeting unmet needs in schizophrenia – non-adherence

- Non-adherence rates are extremely high with schizophrenia therapy
 - ~75% of patients with schizophrenia are non-adherent within 2 years of being discharged from hospital¹
- The consequences of non-adherence are medically (and economically) severe
 - 69% of patients with poor adherence suffer a relapse²
 - (Only 18% of patients with good adherence suffer a relapse²)
- 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

Improving treatment outcomes in schizophrenia

Overall positioning of aripiprazole oral OW

The “best adherence” product

- A once-weekly oral therapy allows “observed dosing” at some level to become a reality for many more patients struggling to adhere to once-daily oral therapy who are in danger of relapse
 - Approximately 70% of schizophrenic patients
- A once-weekly oral therapy allows “observed dosing” by medical staff to become an economically viable option and a therapeutically equivalent alternative for patients who are currently struggling with long-acting depot injection agents
 - Approximately 5% of schizophrenic patients
- A once-weekly oral therapy offers an alternative and more convenient option for all psychotic patients, whether they receive observed or non-observed dosing

Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

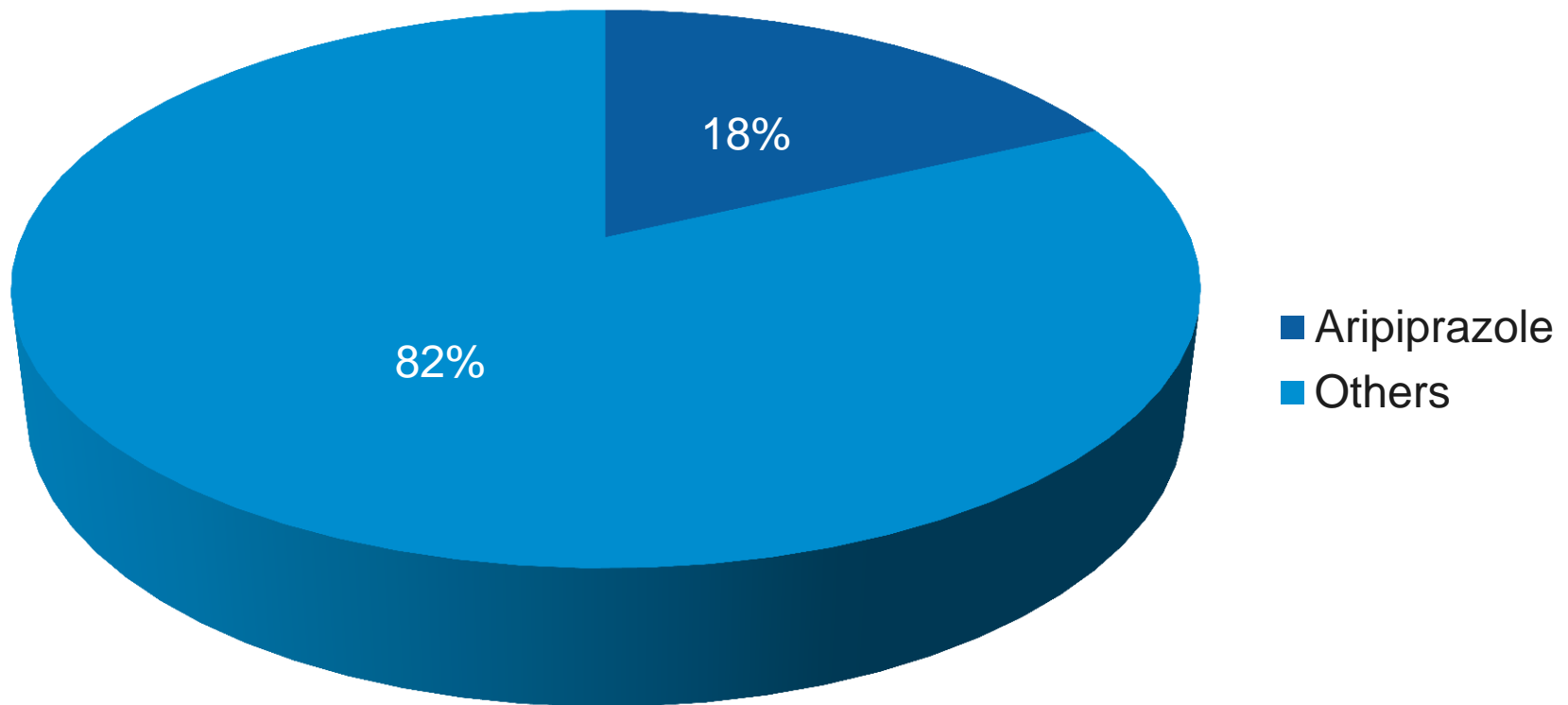
Appendix



Improving treatment outcomes in schizophrenia

Overall market for aripiprazole oral OW

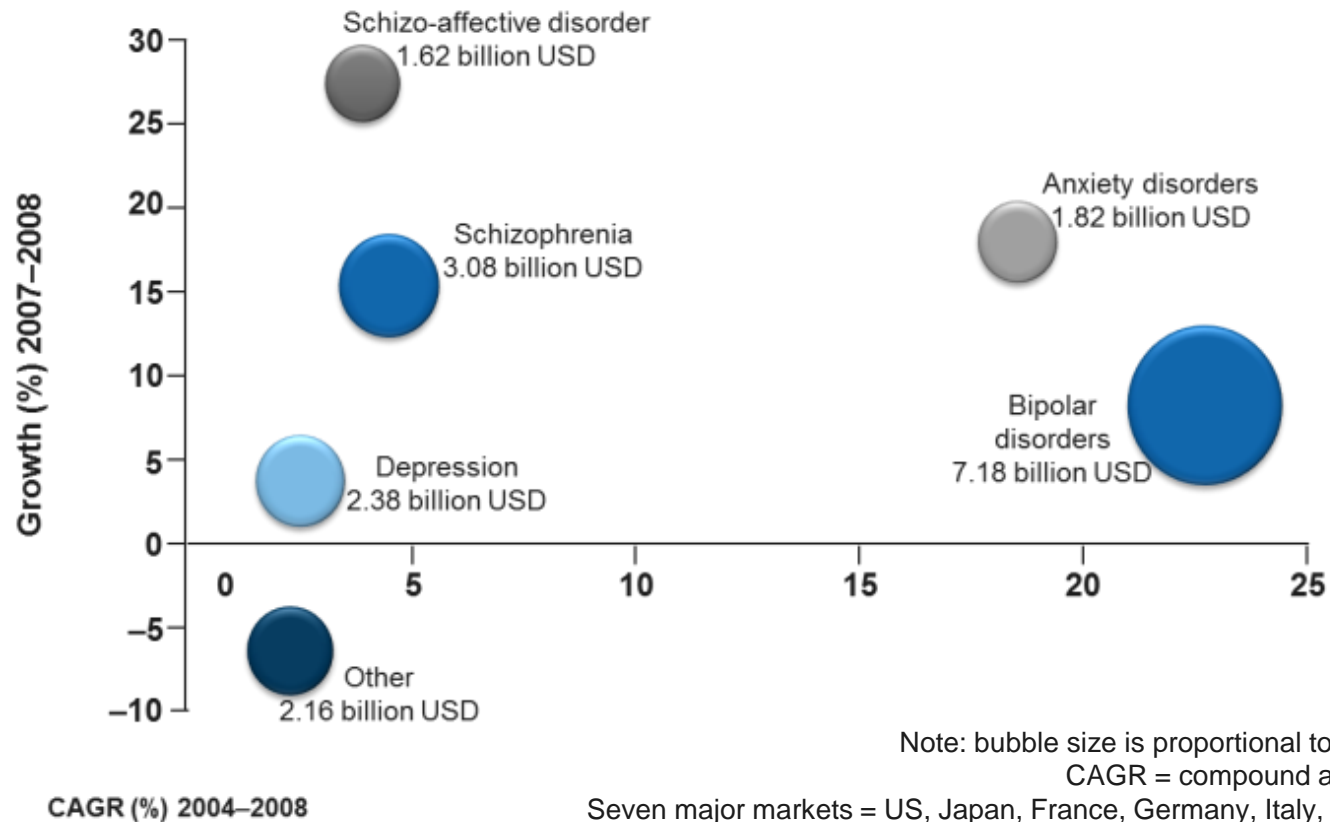
Antipsychotic sales in 2008 were estimated to be 13.4 billion USD



Improving treatment outcomes in schizophrenia

Overall market for aripiprazole oral OW

Antipsychotics are used off-label for a variety of disorders



Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

Appendix



Creating aripiprazole oral OW

Strategy adopted to achieve the goal

A patent-protected, sustained-release formulation

- Aripiprazole is poorly water-soluble, but is intended to be used at a relatively low unit dose strength
 - Hydrophilic matrices with predominant erosion control were selected as the preferred sustained-release (SR) platform
- Control over matrix erosion to achieve consistent SR throughout the gastrointestinal tract was achieved using low viscosity grades of hydroxypropylmethylcellulose (HPMC)
- Development of SR formulations in the absence of drug absorption data from the diverse regions of the human gut is challenging
 - To maximise the chances of clinical success, two distinct SR formulations were developed for human testing, with clearly differentiated in vitro release profiles
- Two year stability data on candidate SR formulations under ICH conditions demonstrated no change in drug release properties or related substances

Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

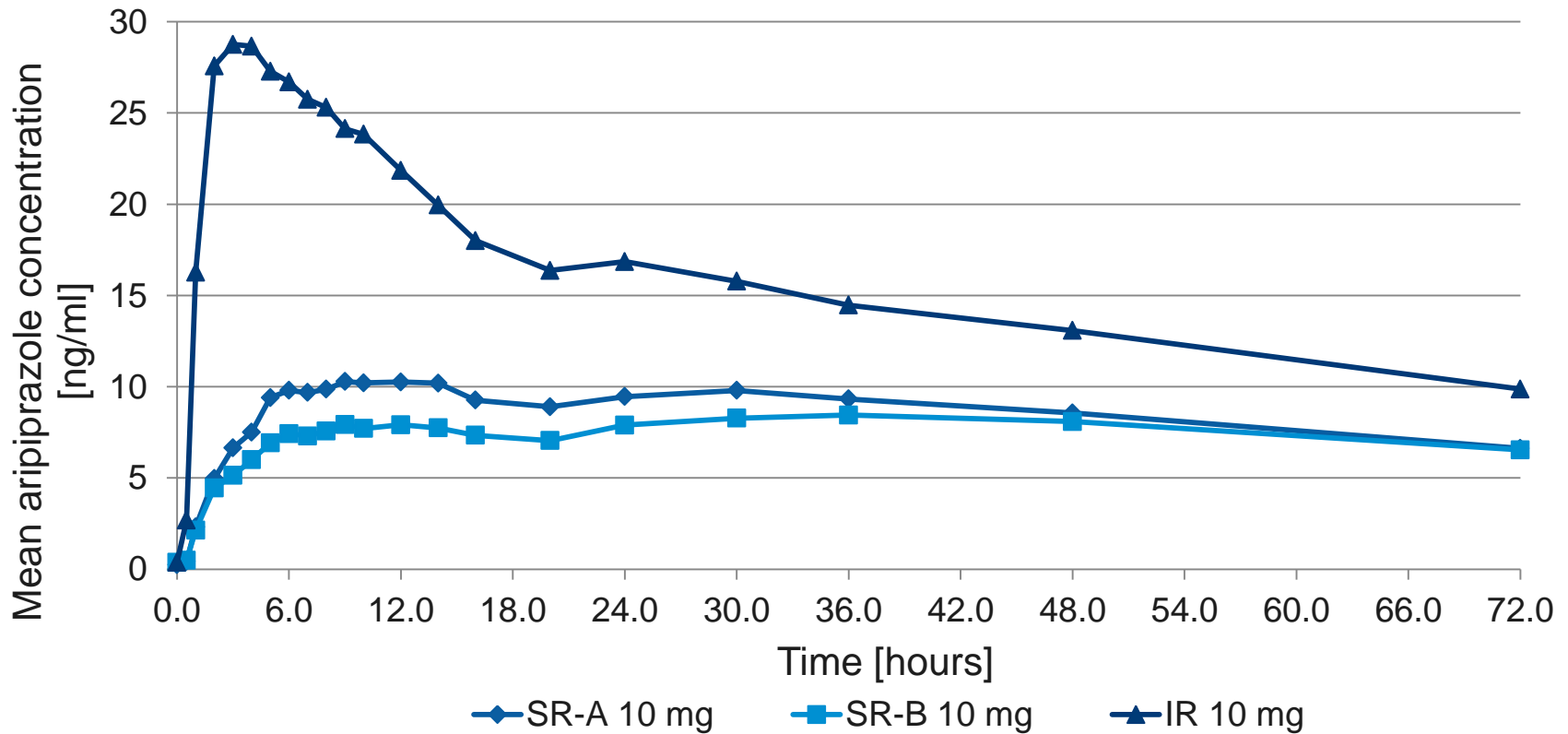
Appendix



Clinical testing of aripiprazole oral OW

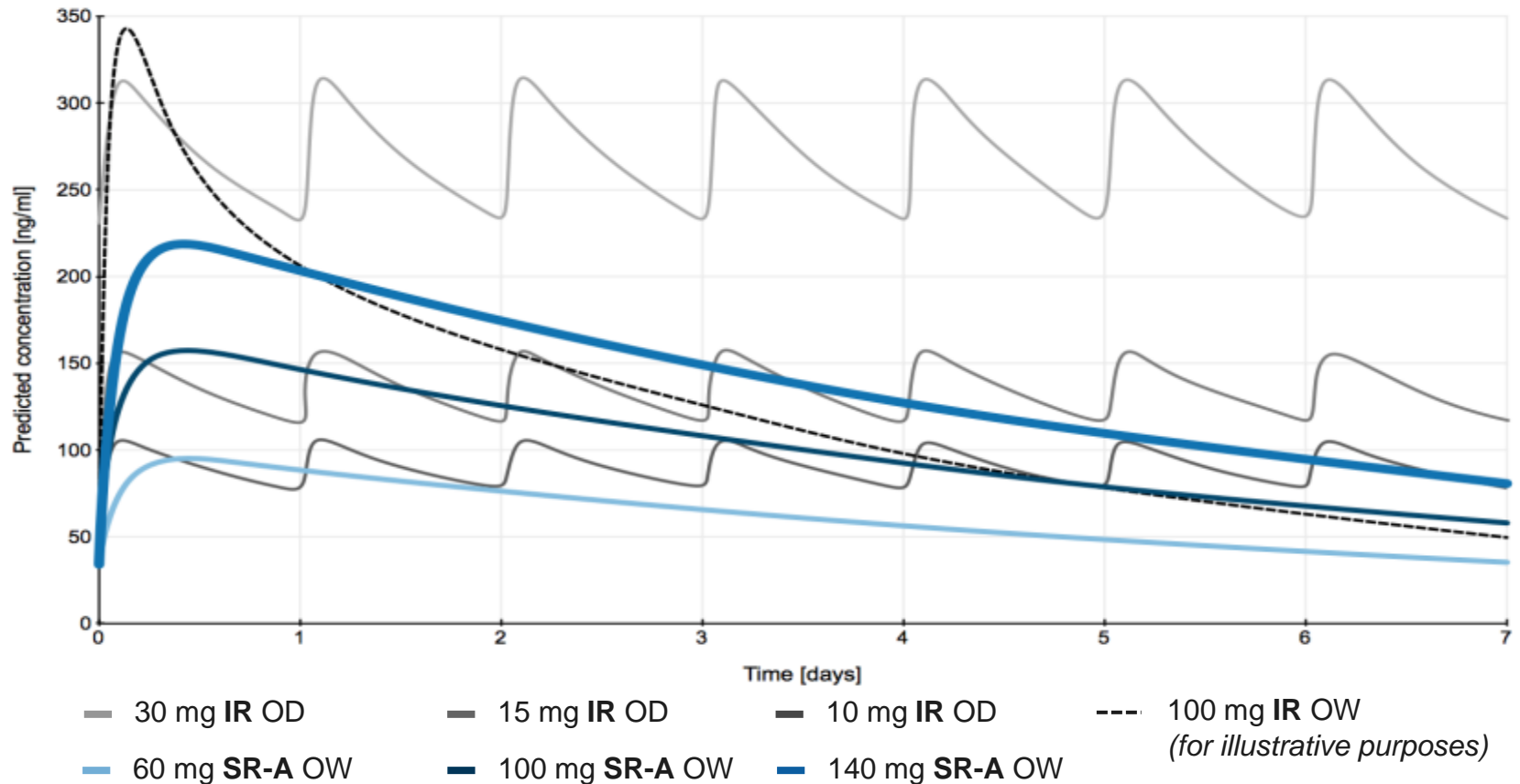
Mean pharmacokinetic performance demonstrates ideal SR profile

Healthy volunteers for SR-A and SR-B vs immediate release (IR) reference



Steady-state pharmacokinetic comparisons

Various IR and SR dosing regimens



Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

Appendix



Receptor-occupancy data extend PK data conclusions

A plasma-brain disconnect exists for aripiprazole dopamine-binding

Aripiprazole dissociation from binding sites is slow

- It is widely accepted that the antipsychotic effects of dopamine receptor antagonists occur within a “therapeutic window” of 60–80% of striatal D2 and D3 dopamine receptor occupancy
- Positron emission tomography (PET) allows the assessment of aripiprazole receptor occupancy in the brain
- Gründer et al. characterised the extra-striatal and time-dependent binding characteristics of aripiprazole using PET imaging at varying time points post-dose with aripiprazole once-daily (OD)
- Aripiprazole at clinical doses occupies a high fraction of its target receptor everywhere in the brain, but its dissociation from those receptors is very slow
- The authors conclude that:

“in patients with serum aripiprazole concentrations in the range typical for clinical practice, D2 and D3 receptors must remain nearly saturated for as long as 1 week after the last dose”

Growing recognition of plasma/brain disconnect

Dissociation between drug brain and plasma kinetics

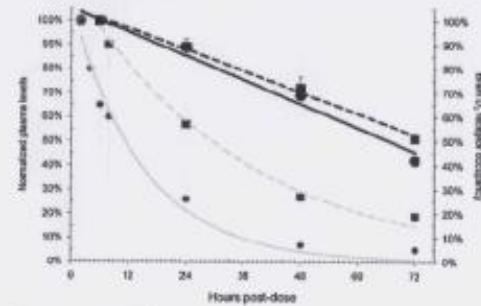


Figure 1 Single dose experiments in controls. Time course of plasma levels (olanzapine: ■, grey dashed line; risperidone plus 9-OH-risperidone: ●, grey solid line), and striatal D₂ receptor occupancy (olanzapine: ■, black dashed line; risperidone: ●, black solid line). All results are normalized to 100% of their peak value. Error bars denote one standard deviation.

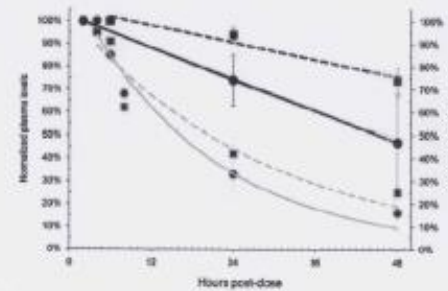


Figure 2 Discontinuation experiments in patients. Time course of plasma levels (olanzapine: ■, grey dashed line; risperidone plus 9-OH-risperidone: ●, grey solid line) and striatal D₂ receptor occupancy (olanzapine: ■, black dashed line; risperidone: ●, black solid line). All results are normalized to 100% of their peak value. Error bars denote one standard deviation.

Tauscher et al, *Molecular Psychiatry* 2002; 7:317

- Question the current reliance on PK
- Support the use of brain kinetics

for dosing schedules



27



Zysis Phase II study design

Comparing the receptor occupancy of aripiprazole OW with OD

Dose-ranging PET study in schizophrenia patients

- This study is a randomised, single-blind, single-centre, multiple group study in 40 schizophrenia patients (as defined by the DSM-IV-TR criteria)
- The **primary objective** of the study is to determine which dose of aripiprazole OW matches D2 and D3 receptor occupancy in the striatum region of the brain at trough (7 days post-dose), compared to aripiprazole OD. The planned dosing groups are as follows
 - Group 1: 60 mg aripiprazole OW (n=10)
 - Group 2: 100 mg aripiprazole OW (n=10)
 - Group 3: 140 mg aripiprazole OW (n=10)
 - Group 4: 15 mg aripiprazole OD (n=10)
- Study will be undertaken with Professor Gerhard Gründer, Pharmalmage and FOCUS Clinical Drug Development

Precedent for use of PET imaging in dose selection

Paliperidone dose range was established using PET imaging data

European Public Assessment Report (EPAR) for paliperidone

“Based on data from PET studies, a relationship between paliperidone plasma concentrations and D2 receptor occupancy was found, and plasma concentrations needed to achieve an effect on schizophrenic symptoms were fairly well defined.

“A dose range for ER OROS paliperidone that would lead to a receptor occupancy of 70–80%, which is likely to be efficacious, was estimated to be between 4.5 and 9 mg (10–20 ng/ml), using the Emax model, while doses resulting in plasma concentrations above 19.6 ng/ml (>80% receptor occupancy) could be associated with a higher incidence of adverse events associated with central D2 receptor antagonism.

“Based on this, the dose range of 3–15 mg ER OROS paliperidone was evaluated for efficacy and safety in the pivotal Phase III studies.”


Zysis Phase III study design

Demonstrating maintenance of efficacy for OW vs OD

Phase III options

- Four possible options for Phase III clinical trials to achieve approval

Phase III options	Patient numbers	Cost [USD]	Time to regulatory submission [years]
No Phase III study	0	0	1.5
Single Phase III study of 6 weeks' drug treatment	625	12.5 million	3
Single Phase III study of 12 weeks' drug treatment	625	18 million	3
Two Phase III studies of 12 weeks' drug treatment	1,250	36 million	4

 Likely Phase III strategy

Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

Appendix



Zysis Phase III study design

Aripiprazole oral OW has a strong intellectual property position

Patent 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
- The patent application entered the national phase of prosecution in key markets (US, Europe, Japan, Israel, Australia, Canada and South Korea) with amended claims in March 2009
- An “intention to grant” letter has recently been received from the European Patent Office
- Current OD patent protection allows launch of oral OW
 - US = 2015
 - EU = 2014

Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market Research

Forecasting

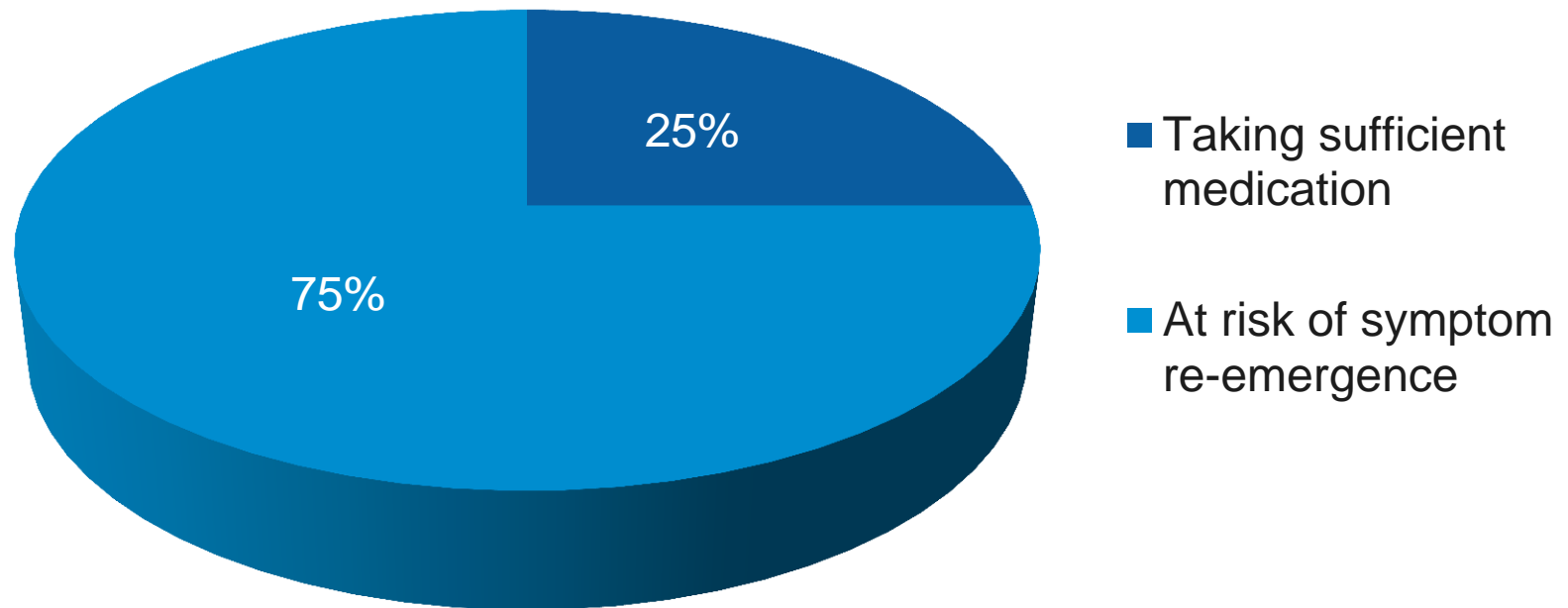
Appendix



The market

Splitting the market by patient adherence levels

- Adherence levels vary within patients; **most** patients are only **partially** adherent **all** the time
- At any one time, approximately **75%** of patients are not receiving enough antipsychotic medication to stop the re-emergence of symptoms



The market

Targeting unmet needs in schizophrenia – non-adherence

Splitting the market by patient adherence levels

- Non-adherence rates are extremely high with schizophrenia therapy
 - ~75% of patients with schizophrenia are non-adherent within 2 years of being discharged from hospital¹
- The consequences of non-adherence are both medically (and economically) severe
 - 69% of patients with poor adherence suffer a relapse²
 - Only 18% of patients with good adherence suffer a relapse²
- 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

The market

Gatekeepers: prescribing decision makers are senior psychiatrists

The antipsychotic market is a specialist-driven market

- The classic pyramidal “Top-Down” selling works for this market



The product

Aripiprazole oral OW “best adherence” product

Features and benefits

Feature	Benefit
Once-weekly oral dosing	Observed dosing is now easier and an economically viable option for many more non-adherent patients in the community
Once-weekly oral dosing	All patients have a more convenient option
Alternative to depots	Greatly reduced direct cost of treatment vs depot injection
Alternative to depots	No need to approach patients with a needle, reducing the risks for medical professionals (and insurers)
Alternative to depots	Most patients prefer oral medicines to injection agents

Promotion

Positioning: aripiprazole oral OW 'best adherence' product

Overall key messages

- Aripiprazole oral OW represents a **first-in-class** antipsychotic agent; it is the only oral once-weekly antipsychotic therapy
- Aripiprazole oral OW allows **better outcomes** for patients by making some level of observed dosing a viable option for patients struggling with non-adherence issues
- Aripiprazole oral OW generates **direct cost savings** by improving adherence (thereby reducing frequency of relapse) and reducing medical staff costs
- Aripiprazole oral OW provides a **more convenient** option for all patients
- Aripiprazole oral OW, with observed dosing, is a **viable alternative** to depot injection agents at a fraction of the cost

Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

Appendix



Pricing and cost-effectiveness

Key concepts to build a strong cost-effectiveness argument

Achieving relapse rates equal to risperidone depot injection

- For patients who do not adhere well to therapy
 - Observed dosing by medical staff should achieve adherence rates equal to risperidone depot injections in the hospital and community clinic setting (e.g. utilising existing clozapine clinics) for more severe patients
 - Counsellor-/psychologist-observed dosing should achieve adherence rates approaching risperidone depot injections in the ongoing community care setting
 - Family-/carer-/friend-observed dosing is expected to be measurably better than non-observed dosing rates
- For non-observed patients and those who adhere well to therapy
 - Non-observed oral OW dosing is expected to generate better levels of adherence than oral OD therapy, and therefore reduce symptom relapse rates

Aspects of pricing unique to antipsychotics

Aripiprazole oral OW is unlikely to be reference priced in most major markets

- In the USA, “the centers for Medicare and Medicaid services (CMS), recognising the potential for adverse outcomes, require Medicare Part D plans **to cover all or substantially all** drugs in three classes of psychiatric medications: antipsychotics, anticonvulsants and antidepressants.”
- In Germany, there is no reference pricing for atypical antipsychotics
- In the UK, Italy, Spain and most other European countries there is no pricing restrictions on prescribing of antipsychotics beyond an ‘overall budget for antipsychotics’ per region

However, if aripiprazole is reference priced by 2015

- Two versions of an aripiprazole depot injection are due to be launched in 2015
- Reference pricing aripiprazole oral OW to these as an ‘alternative oral depot’ will strengthen the argument for a small increase in price over oral OD

Aspects of pricing unique to antipsychotics

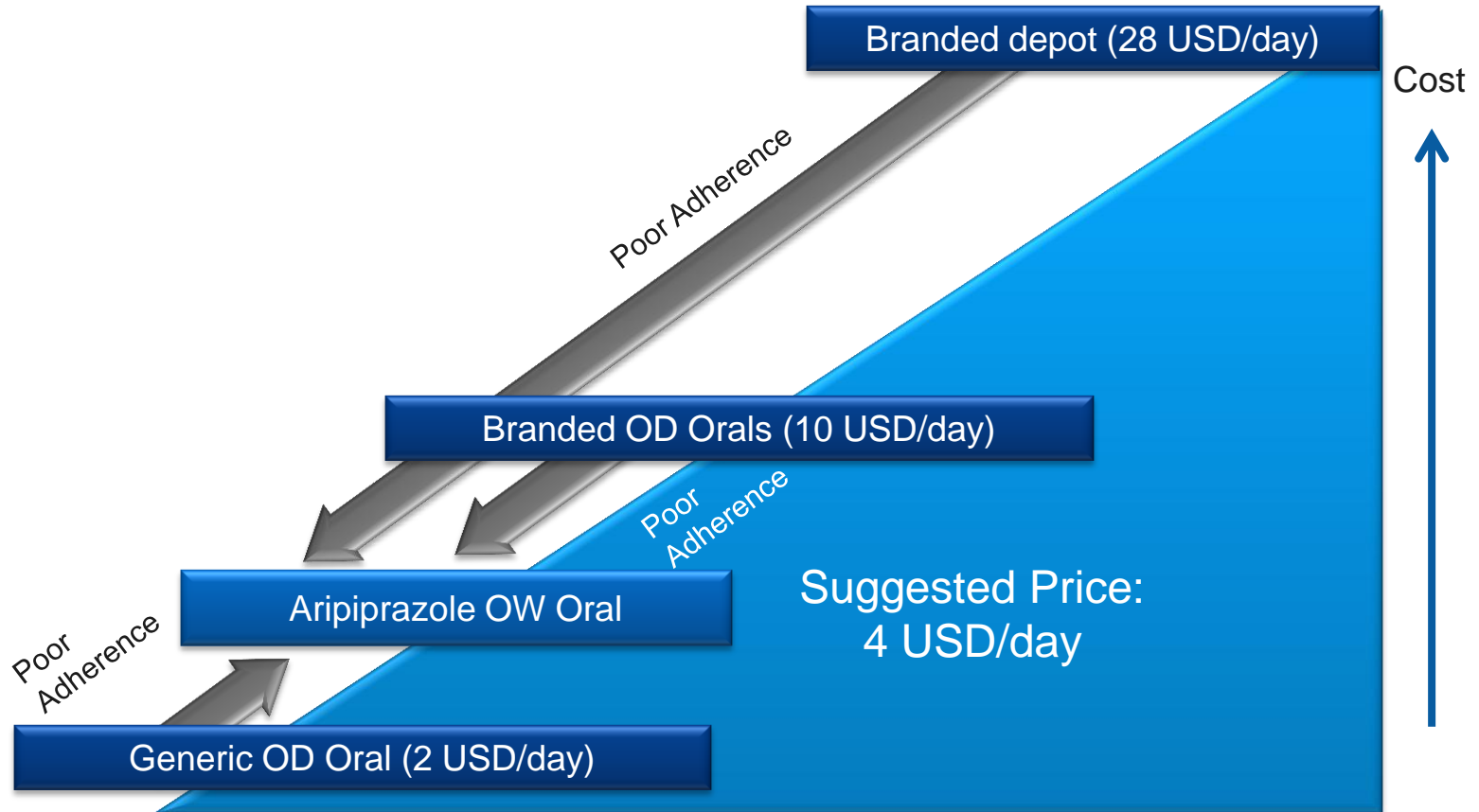
National Institute of Clinical Excellence (NICE) in the UK encourages the use of treatments which reduce relapse

- *“The updated guideline encourages greater adherence by increasing people’s understanding and involvement in the choice of drugs.*
- *“Studies (Knapp, et al.) have shown that increased adherence reduces healthcare costs through a reduction in relapse/acute episodes, and subsequent hospitalisation rates.*
- *“These cost savings may be offset against any increases in drug costs”*

Pricing and cost-effectiveness

Balancing highest price for optimal market penetration and profitability

Aripiprazole OW Oral is an “oral depot” for pricing purposes



Pricing and cost-effectiveness

Justifying a 4 USD per day price

Zysis cost-effectiveness model in schizophrenia

Cost savings per patient per year	USD
Cost savings are evident with mixed aripiprazole oral OW therapy* when compared to:	
Generic oral OD	813
Branded oral OD	3,368
Generic depot injection agents	1,529
Risperidone depot injection	3,343

- The costs of schizophrenia therapy are driven by the cost of relapse
- A treatment paradigm that improves relapse rates can justify a higher price (compared with risperidone depot injections)

**Mixed aripiprazole oral OW therapy assumes a mix of observed dosing – some patients are non-observed, others are observed in the community, and some are observed in a clinical setting*

Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

Appendix



Market research amongst physicians

Market analysis performed to date

Two key target audiences

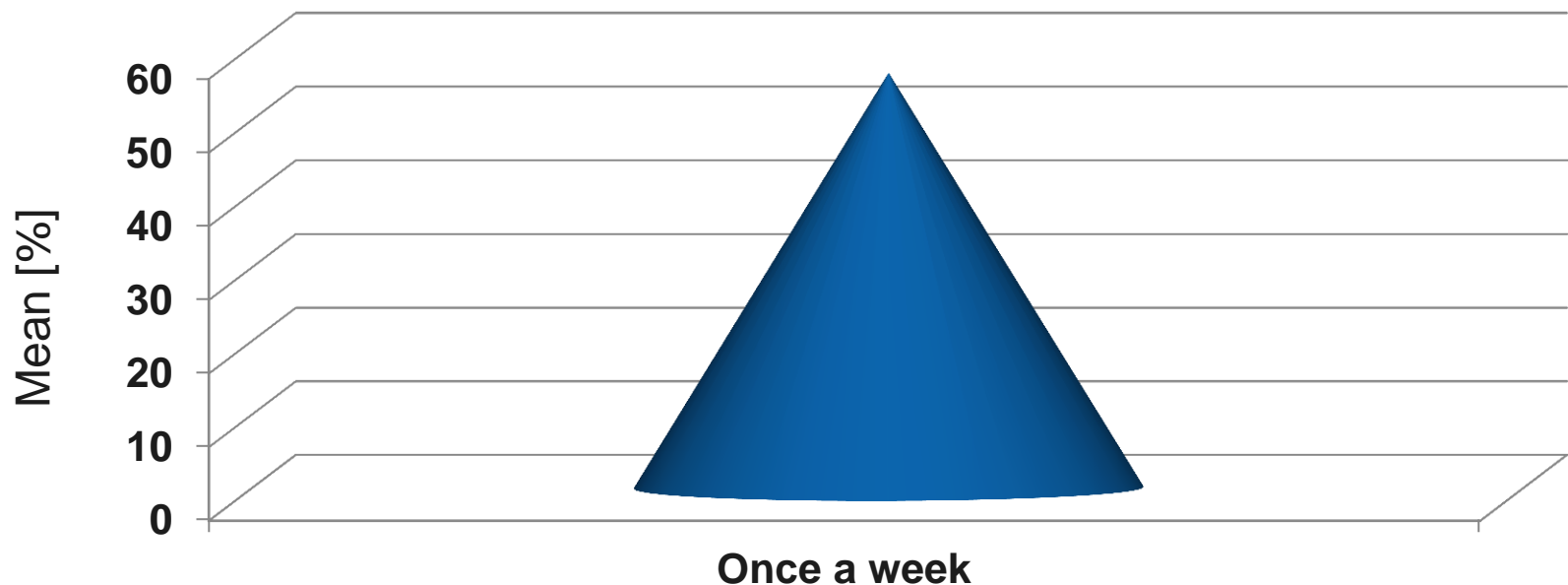
- Key opinion leaders
 - Zysis has directly approached key opinion leaders, through one-to-one contact, in several key countries across Europe, North America and Australia, and assessed their opinions
 - A variety of media have been used: email, telephone, direct interviews and advisory panel group discussion
- Prescribing decision makers
 - Senior psychiatrist decision makers were interviewed by questionnaire through conference research in April 2008
 - The attractiveness of an oral OW therapy and the likelihood of the physicians to prescribe it were analysed

Market research

Prescribing decision makers

Sample: 30 senior psychiatrists (mainly US, Europe)

- What proportion of your maintenance patients might you prescribe an aripiprazole oral OW product if it were to become available?



Physicians felt that they would prescribe an oral OW therapy for 55% of their maintenance patients

Market research

Key opinion leaders

Quotes:

- “Aripiprazole has both a different mechanism and a much broader spectrum of action (depression, mania and antipsychotic) so the population that is likely to be considered for this drug is larger than the typical antipsychotics. Even if there are no studies done for patients from these diagnostic categories, it is likely that physicians will use it in that way anyway, since it is known to work for those illnesses. So, I think that there is a significant population that could benefit from this new drug.”
Dr Richard McCarthy, New York, USA
- “I agree on the potential target population and would like to remark that, besides the non-adherent patients who can be as many as 40% of bipolar patients (similar in schizophrenia) or even more in some settings, there are also those patients who are ‘potential candidates for non-adherence’. Those are patients who may be taking the medication today but might change their mind in the future. Rates are then much higher than 40% and up to 80%.”
Prof Eduard Vieta, Barcelona, Spain/Boston, USA
- “Adherence is one of the most important problems with antipsychotic treatment, and it is very difficult to be sure if patients take the prescribed oral medications. In addition, there is a proportion of patients that do not like injectable preparations. Once a week is a very friendly way of taking a drug and family can easily control the intake of medication if needed.”
Prof Maria-Luisa Figueira, Lisbon, Portugal

Market research

Key opinion leaders

Quotes:

- “Sounds a good product, non-compliance is a huge issue; anything that helps is a good thing. If it works then why would any patient take daily meds? If people could take a lipid-lowering drug once a week rather than daily then most, if not all, would. I see a lot of refractory patients so aripiprazole OD isn’t used as much, but in general psychiatry I would be tempted to try it in most people that I would be happy putting on aripiprazole; so around 30–40%. And perhaps more in first-episode patients, as I would like the idea of low metabolic and EPS side effects.”
Prof Sukhi Shurgill, Institute of Psychiatry, UK
- “Adherence is an important issue for clinical practice. Aripiprazole once-weekly could be particularly useful for patients with partial adherence, or in order to simplify drug administration in non-adherent patients.”
Prof Giulio Perugi, Gerona, Italy
- “Adherence is a big issue and contributes significantly to poorer outcomes in schizophrenia and bipolar disorder. I agree that the potential market for a weekly oral antipsychotic would likely be significant, and that an accompanying ‘compliance’ package would be a good thing to think of.”
Prof Allan Young, Imperial College, London, UK
- “I think the possibility of a once-weekly oral medication would be a great boon for early psychosis and for all patients. Very exciting and hopefully not too good to be true!”
Prof Pat McGorry, Melbourne, Australia, Australian of the Year 2010

Market research

Key opinion leaders

Quotes:

- “A once-weekly formulation of aripiprazole would be a great advantage, of course. It would be a genuine, and more loved, alternative to depot medication in patients with adherence problems. My guess would be that >50% of aripiprazole patients would prefer to switch to it, and probably up to 20% of patients on other oral atypicals. For those patients where text message reminders or involvement of relatives are not sufficient, a weekly visit of the community psychiatric nurse or, in Germany, visiting your GP or psychiatrist should be possible – this category of patients may be so ill that they are seen regularly anyway. Uniquely to Germany, psychiatric patients see their psychiatrist more frequently, or at least the staff of the practice, e.g. for depot injections. Actually, the most frequently used depot in Germany is a weekly depot fluspirilene injection, so seeing the GP or psychiatrist practice once-weekly is already an established routine.”
Prof Heinz Grunze, Newcastle, UK (previously Munich, Germany)
- “Very long-acting oral formulations of antipsychotic medications are desperately needed. Most of the patients are non-compliant most of the time, which is why they are forever relapsing and requiring readmission, crisis and intensive home treatment, etc.”
Prof Ann Mortimer, Hull, UK
- “Actually, I think this treatment would be very useful for a substantial population of patients, especially bipolar ones for whom no long-acting preparation is licensed in France.”
Prof Jean-Michel Azorin, Marseilles, France

Market research

Key opinion leaders

Who are these experts?:

- **Dr Richard McCarthy, New York, USA** – clinically-focused/practical expert, focused on treatment of moderate to severe patients in the community
- **Professor Eduard Vieta, Barcelona, Spain/Boston, USA** – world-recognised leader in bipolar disorder drug development and clinical trial work. Associate Professor at Harvard, Boston
- **Professor Maria-Luisa Figueira, Lisbon, Portugal** – has been the leading psychiatrist in Portugal for many years. Runs a very busy clinical department as well as extensive research interests. Head of the Psychiatric Department of the Hospital Santa Maria at the University of Lisbon
- **Professor Sukhi Shurgill, London, UK** – rising star in the largest psychiatric research and treatment centre in Europe. Second tier down from the top level at the Institute of Psychiatry
- **Professor Giulio Perugi, Head of Department, Gerona, Italy** – has just accepted the most influential and well-respected psychiatry position in Italy
- **Professor Allan Young, London, UK** – probably the leading light of his generation in bipolar disorders in the UK. Runs both research and clinical departments at Imperial College, London; taken over from Professor David Nutt
- **Professor Pat McGorry, Melbourne, Australia** – President of the International Early Psychosis Association, and named Australian of the Year 2010. One of the leading psychiatry professors in Australia
- **Professor Heinz Grunze, Newcastle, UK** – acknowledged bipolar disorders clinical trial expert, used to run a tertiary referral centre at Munich University
- **Professor Ann Mortimer, Hull, UK** – practical schizophrenia expert. Runs a severe patient clinic in Hull, as well as extensive research interests
- **Professor Jean-Michel Azorin, Marseilles, France** – President of the French Psychiatry Association, and an expert in bipolar disorder

Market research

Overview

For key target audiences

- International and national key opinion leaders and influencers
 - Positive about an oral adherence benefit product
 - Estimated 30–40% (or $\leq 80\%$) patients would be suitable/benefit
 - Identified patient segments immediately
 - Early psychosis, non-adherers, bipolar, severe symptoms, etc.
 - Felt an added-adherence package could work well alongside the product
 - Considered off-label usage to be a vast opportunity too
 - Immediately suggested family-supported observed medication administration without prompting
 - Identified intensive home treatment as an issue with relapsing patients
 - **This fits with the desk research data**
- Prescribing decision makers
 - Identified 55% of patients as suitable for an aripiprazole oral OW therapy

Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

Appendix



Forecasting

Overview

Assumptions

- Aripiprazole oral OW can target the whole maintenance segment (85% of the antipsychotic market)
- Aripiprazole OD currently holds 18% market share, but is still growing strongly
- Based on Zysis marketing research projects, psychiatrists estimate around 30–55% of patients would be prescribed an aripiprazole oral OW formulation
- Zysis estimates a market share of 8–12% by volume when promotional weighting is taken into account
- On this basis, peak year sales of approximately 600 million to 1 billion USD are thought to be achievable

Aripiprazole oral once-weekly

Introduction

Market proportions

Technical overview and reformulation

Clinical trial activity and computer modelling

Clinical trial plan to approval

Intellectual property position

Marketing assessment and promotion

Pricing

Market research

Forecasting

Appendix



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**
 - Spent 14 years in large pharmaceutical Sales & Marketing, including the global launch of three psychiatric drugs
 - Founder of Cortex Congress Neuroscience Conference company; 10 years of establishing and managing conferences in psychiatry and neurology