#### EXHIBIT 6

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From: Birkett, Geoff

Sent: Tuesday, March 04, 2003 7:44 PM

To: Bierczynski, Vicky B

Subject: FW: Schizo SSF 3.04

Attachments: Schizo SSF 3.04.ppt

pls do neat colour copy for tomorrow

-----Original Message-----

From: Wilkie, Alison M

Sent: Tuesday, March 04, 2003 2:28 PM

To: Birkett, Geoff

Cc: Bierczynski, Vicky B

Subject: Schizo SSF 3.04

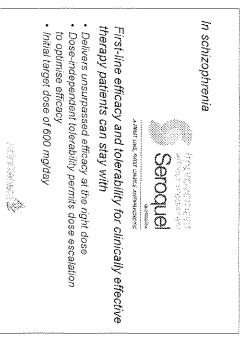
Bickett	
EXHIBIT NO.2	1 Hostorensing
ANK 4/24/08	

Geoff

Here is the 'tweaked' version for John tomorrow - please let me know if you have any questions.

thanks

Alison



the treatment of schizophrenia. The following pages represent a core detail flow and backup data that support our current position for Seroquel in

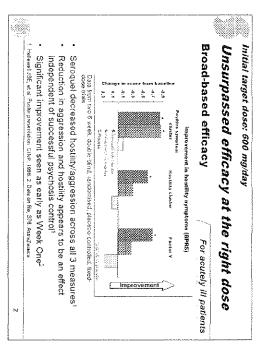
#### The detail flow

The detail flow presents a succinct summary of the strongest data from our best studies to support Seroquel as the binsufpassedeeffiquical antip sygluodosevith

- Dose-independent tolerability that permits dose escalation to optimise efficacy
- At the right dose-starting with an initial target of 600 mg/day-Seroquel offers unsurpassed clinical effectiveness
- The target 600-mg/day dose is flagged on every page showing efficacy data

#### Backup data

approved for marketing purposes. Backup data are supplied so that local markets can either expand on the data in the core detail or substitute data



worsening other primary symptoms. The symptom spectrum for schizophrenia includes aggression and hostility, which need to be controlled without

## Key communication

On this page In addition to managing positive and negative symptoms, Seroquel effectively controls aggressive/hostile symptoms

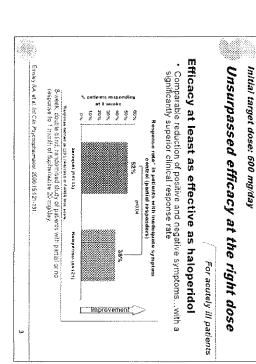
- The graph shows Seroquel efficacy in controlling symptoms compared to haloperidol and placebo
- The second bullet notes that, although Seroquel controlled positive and negative symptoms in these studies, improvement in aggression/hostility was an independent effect
- The third bullet emphasises the rapid onset of symptom control

#### About the study

- Data from two 6-week, well-controlled trials. One trial compared 5 different doses of Seroquel to haloperidol 12 mg/day or placebo. The other trial compared low doses (up to 250 mg/day), and high doses (up to 750 mg/day) to placebo
- Seroquel 600 mg/day was associated with the most consistent improvement
- Scroquel produced greater improvement than haloperidol, but differences were not statistically significant. In addition, changes vs placebo were significant at certain points for Seroquel, but not for haloperidol

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Seroquel and haloperidol have been compared in a number of studies. The Emsley study compares these agents in patients with partial treatment failure on other medication

## **Key communication**

better clinical response Head to head with haloperidol, Seroquel offers the same-or better-efficacy, and the added advantage of a significantly

#### On this page

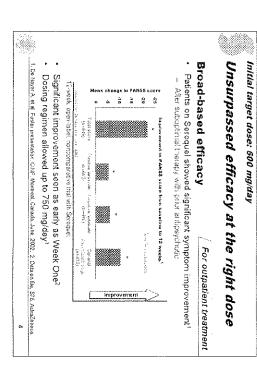
- The graph shows that Seroquel had a significantly better response rate (patients with a  $\geq 20\%$  reduction in PANSS score) than haloperidol
- The bullet highlights the Seroquel advantage-equal efficacy, superior response

## About the study

- to fluphenazine An 8-week, well-controlled trial of 288 patients who had partial response to typical antipsychotics and no response
- Seroquel showed marked reduction in PANSS scores greater at Week 8 and Week 12 than haloperidol, although these scores did not reach significance

# CGP. Other a protocol and the set of the protocol and the set of the set of

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control a range of schizophrenia symptoms, including 2 of the most critical kind-positive and negative symptoms The detail flow starts with efficacy. Seroquel efficacy has been proven in numerous well-controlled clinical trials to

## Key communication

antipsychotic medication Seroquel significantly improved key symptoms of schizophrenia in patients unsuccessfully treated with another

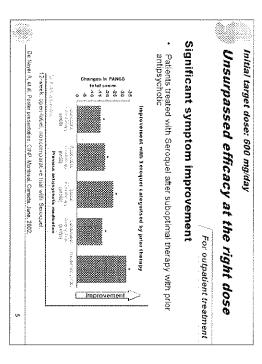
#### On this page

- This graph shows data from the SPECTRUM study, illustrating the change in PANSS scores for all patients
- The next page shows improvement categorised by prior suboptimal treatment
- The second bullet emphasizes rapid onset of improvement---within 1 week
- The third bullet reinforces efficacy at the right dose

#### About the study

SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel

Usual Medication. PANSS: Positive and Negative Syndrome Scale. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to



The advantages of switching patients to Seroquel from current therapy support its use as a first-line choice.

## Key communication

Seroquel, and get the right efficacy from the beginning? Seroquel improves efficacy, no matter what antipsychotic agent was used prior. So why not start patients on

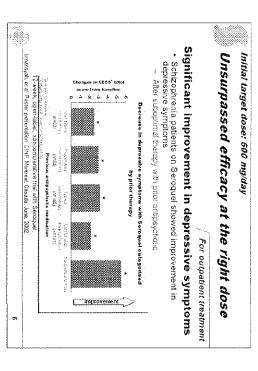
#### On this page

 This graph demonstrates that, no matter which antipsychotic a patient was switched from, Seroquel provided symptom improvement (as measured by PANSS)

#### About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel
- Study results show that patients who were started on Seroquel due to partial or no response on previous medication showed symptom improvement and a reduction in EPS side effects
- Similarly, patients who were started on Seroquel because of intolerance to the side effects of their previous medication not only showed a reduction in side-effect incidence, but an improvement in efficacy

Changing Treatment Relative to Usual Medication. EPS: Extrapyramidal symptoms. PANSS: Positive and Negative Syndrome Scale. SPECTRUM: Seroquel Patient Evaluation on



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a valuable treatment choice. An antipsychotic that can help treat depression, as well as positive, negative, and other symptoms of schizophrenia, is

## **Key communication**

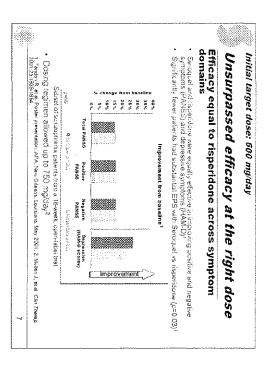
Unprovement with a switch to Seroquel includes reduction in depressive symptoms.

This graph demonstrates that, no matter what antipsychotic patients were switched from, Seroquel provided improvement in depressive symptoms

#### About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were started on Seroquel
- While improvement was seen regardless of whether patients were evaluated as depressed when they started Seroquel improvement was especially noticeable in patients classified as depressed at baseline

SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Data from QUEST compare the symptom relief of Seroquel and risperidone

## Key communication

Seroquel improved positive, negative, and depressive symptoms significantly better than risperidone

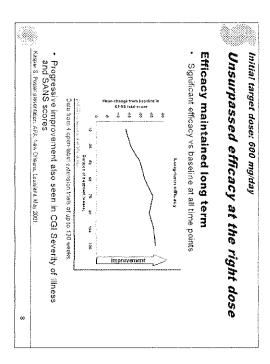
#### On this page

- The graph, from the QUEST study, shows improvement in PANSS scores and depressive symptoms in a subset of patients with schizophrenia
- The bullet below the graph notes that dosing went as high as 750 mg/day in this study

#### About the study

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone
- · A subset of patients with schizophrenia was also analysed

HAM-D: Hamilton Rating Scale for Depression. PANSS: Positive and Negative Syndrome Scale. QUEST: Quetiapine Experience with Safety and Tolerability.



A chronic condition like schizophrenia requires treatment that stays effective long term.

## Key communication

Seroquel maintains effective control of symptoms for the long term.

#### On this page

- The graph plots improvement in total BPRS score (which includes positive and negative symptom measures, as well as 16 other items) over 130 weeks
- measured by CGI, and negative symptoms, as measured by SANS The second bullet highlights that, in addition to improving BPRS score, Seroquel therapy improved severity of illness, as

## About the study

- Data analysis for 674 patients in 4 open-label extension trials lasting up to 130 weeks
- Efficacy and tolerability were assessed

BPRS: Brief Psychiatric Rating Scale. SANS: Scale for the Assessment of Negative Symptoms. CGI: Clinical Global Impression.

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The ONLY first-line atypical with EPS (including akathisia) no different from placebo at any recommended dose Risperidane Prescribing Information, 2. Clanzapine Prescribing information, 3. Arvanite LA, et al. Gial Psychiaty 1997;42:253-246. Dose-independent tolerability permits dose escalation to optimise efficacy Some other antipsychotics (including olanzapine, risperidone) show dose-related EPS increases<sup>1,2</sup> 5-week, randomised, double-blind, placebo-controlled study of patients with acute exacerbation of schizophrenia. nietpat un de s ents G 20% Placebs 75 mg 0-51 neidence of overall EPS events<sup>3</sup> p= 53 150 rag 300 rag 8248 12:32 669 mg 758 mg 1,974 20-14 ග

best-known attributes of Seroquel therapy. many antipsychotics that interferes with patients' daily function and compliance. Placebo-level EPS is one of the After efficacy, the detail flow reinforces the well-known Seroquel safety profile, starting with EPS-a side effect of

## Key communication

Seroquel is the only first-line atypical with EPS no different than placebo at any recommended dose

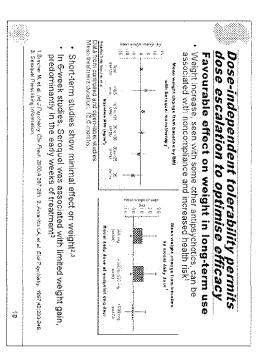
#### On this page

- The graph shows that incidence of EPS barely changed across Scroquel doses in the study, from the lowest dose (75 mg/day) to the highest dose (750 mg/day)
- The bullet refers to the risperidone and olanzapine PIs, which show increased EPS incidence with increasing doses
- Other EPS-related data can be found in the backup section

#### About the study

- A 6-week, well-controlled study of patients randomised to 1 of 5 fixed doses of Seroquel (n = 255), 12 mg haloperidol (n = 50), or placebo (n = 51)
- EPS evaluation was measured by SAS (modified to include akathisia) and AIMS
- AIMS: APROPORTIDAY AND A CONTRACTORY AND A CONTRACT SAS: Simpson-Angus Scale.

haloperidol-37%



noncompliance Weight gain is a side effect clearly associated with certain antipsychotics, and can be a primary reason for patient

## Key communication

Seroquel, unlike some other antipsychotics, is not associated with meaningful weight gain, either in the short or long Winter across the recommended dosing range

- The left-hand graph evaluates weight gain over a mean treatment duration of 18 months in patients grouped by baseline BMI category
- The right-hand graph shows weight change categorised by 3 dosing ranges
- Overall, there was almost no mean change in weight. Interestingly, in underweight patients (BMI  $\leq 18$ ), there was beneficial weight gain, while the most overweight groups (BMI 30-35) lost weight

## About the study

- Long-term weight-change data for 427 patients were pooled from controlled and uncontrolled studies as well as from their open-label extensions
- In these studies, Seroquel monotherapy was the only antipsychotic treatment allowed BMI: Body Mass Index.

EPS: Extrapyramidal symptoms



Placebo-level prolactin at any recommended dose "Data powled from RexSile and Specialcose tites: 1.5. 2021; A. et al. 2017; Junice - Maria 2024 (2.3. August 2.3. Futo prescribed: APA Turite Carola real reve Low incidence of sexual or hormonal side effects with Seroquel<sup>\*2</sup> Dose-independent tolerability permits dose escalation to optimise efficacy l chaoge konntravion (naimil) á Ń C N & C D Š G-week, randomised, double blind, gracebo controled study of patients with acute exacetbation of solitophrenia. Placebo 2.0 1.2 1243 0 mg 15d mg 4100 Gitaixia in prolactio invens -0.5 1220 ÷. Shu nas 1 total с х քա որք 4 X 0 W -0.B 5 w 0 4 7. -1,8 07 ZB <u>...</u>

Abnormal prolactin levels are a common adverse event caused by antipsychotic medication.

## Key communication

As with EPS, prolactin levels in patients taking Seroquel are no different than with placebo across the dosing range

#### On this page

- The graph shows the minimal change in prolactin levels with Seroquel treatment
- The bullet, from a study by Goldstein, confirms that placebo-level prolactin means minimal risk of sexual or hormonal dysfunction

## About the study

- A 6-week, well-controlled study of patients randomised to 1 of 5 fixed doses of Seroquel (n = 255), 12 mg haloperidol (n = 50), or placebo (n = 51)
- · In contrast to Seroquel, the difference in prolactin levels between placebo and haloperidol was significant

S CARGE WITH AL MITHAN LOOM.		
No dosing adjustments required for differences in gender, race, body	No dosing adjustments required for differences in gender, rad weight, or smoking status. May be taken with or without food	No dosing adj veight, or sm
	600 mg	• Day 7:
	400 mg	• Day 5:
	300 mg	• Day 4:
	200 mg	• Day 3:
	100 mg	• Day 2:
	50 mg	• Day 1:
	Dosing initiation <sup>1-3</sup>	Dosing i

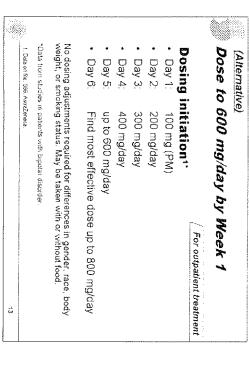
Standard dosing initiation achieves the initial target dose of 600 mg/day by Day 7.

## Key communication

Dosing to 600 mg/day is simple and fast.

#### On this page

• Physicians are familiar with the dosing schedule from the Prescribing Information for Seroquel



The "four by four" dosing approved for treatment of bipolar mania gets patients to 600 mg/day at Day 5.

## Key communication

An accelerated dosing schedule for Seroquel has been proven safe and effective in clinical studies.

Ì. Smith MA, et al. Poster presentation, WUDEU Annual Meeting, Boos Raton, Floring, June, 2002. Low incidence of treatment-related adverse events, most of which were mild to moderate
 Overall frequency of events was similar, whether 400 mg/day was achieved by Day 2 or Day 5 (standard dosing regimen) 400 mg/day dose at Day 2 For acutely ill patients Rapid initiation in hospitalised patients 100 mg 200 mg/day AM Day 1 100 mg PM 200 mg 400 mg/day Day 2: 200 mg ۶<u>۸</u> 600 mg/day 200 mg Day 3: 2 x 200 mg PM 4

profile to traditional dosing schedules For acutely ill patients, an even more rapid target dose initiation has been shown to have a comparable tolerability

## Key communication

Seroquel can be dosed up to 600 mg/day in fewer than the standard 5 days with safety and tolerability. About the study

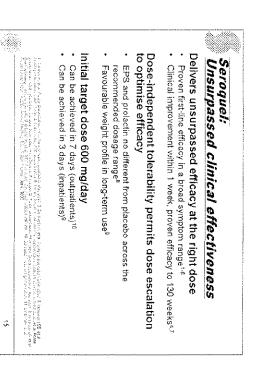
- This was a 5-day, multicentre, double-blind tolerability/safety study of 69 acutely ill schizophrenia patients randomised to 1 of 3 titration arms
- Patients were dosed to 400 mg/day of Seroquel in 5, 3, or 2 days. Patients were hospitalised during their 2-day washout and 5-day treatment periods
- Frequency of adverse events was similar between the 3 groups. Treatment-related events were few, and most were mild to moderate
- Less than 15% of patients experienced somnolence, with the fewest (8%) in the

2-day titration group

Laboratory values and vital signs were also similar amongst the treatment arms, including for blood pressure and pulse measurements

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This page summarises the key communications in the core detail.

16

Back-up slides

Unsurpassed efficacy at the right dose Seroquel significantly improved all BPRS components **Broad-based efficacy** Initial target dose: 600 mg/day Data on fits, 271. AstraZeneca. 1 baseline 60 8 00 3<sup>6</sup> 3<sup>6</sup> 3<sup>6</sup> powar ny pasaoo 2 Placeoo (n=198) & Secesset 140 to 750 mg/day (n=425) (noati ve pasaoa (nais) (nais 20% -20% 50 improvement vs placebs le components of SPRS total score 13 ağıng tötər. 192 Anerge Theaght cisturation Heating Intorovement ٦٢

Additional material on efficacy includes secondary symptoms of schizophrenia.

## Key communication

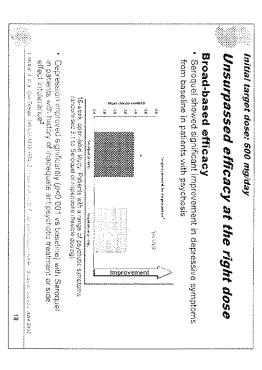
Seroquel effectively manages a wide range of symptoms. On this page

 Seroquel efficacy in controlling 4 individual symptoms comprising the BPRS, with significant differences vs placebo for each

## About the study

- Mcta-analysis of three 6-week, well-controlled published studies
- · Dosing regimens were different for each study

BPRS: Brief Psychiatric Rating Scale.



Data from QUEST support the proven relief of depression with Seroquel

## Key communication

**Ownthispagene** In patients treated for a range of psychosis symptoms, Seroquel improved depressive symptoms significantly better

- The graph, from the QUEST study, shows improvement in depressive symptoms in all patients in the study (ie, all forms
- The bullet below the graph refers to the SPECTRUM study, in which patients with schizophrenia who were unresponsive of psychosis), measured by change in HAM-D scores
- or intolerant to other antipsychotics were started on Seroquel monotherapy

## About the studies

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone
- 641 patients from QUEST were evaluated for depressive symptoms
- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were

intolerant to other antipsychotics were started on Seroquel flexible dosing HAM-D: Hamilton Rating Scale for Depression. QUEST: Quetiapine Experience with Safety and Tolerability. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication



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This was a cohort from a 52-week study of patients on fixed-dose Seroquel, haloperidol, or placebo

About the study

On this page than haloperidol

function

Seroquel 600 mg/day improved cognitive function significantly better

Improvement in cognitive function can help patients recapture functions critical to basic day-to-day tasks

Velligan Di, et al. Schlzophr Res. 2002;53:239-246.

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Collort from a 52-week, double biry, fixed-dose that

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Week 24

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mprovement

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**Broad-based efficacy** 

Cognitive changes were independent of concurrent symptom improvement or lower EPS incidence Cognitive improvement was significantly better with Seroquel 600 mg/day than with haloporidol  $(\rho{<}0.02)$ 

inversement of cognitive dysfunction

Unsurpassed efficacy at the right dose

Initial target dose: 600 mg/day

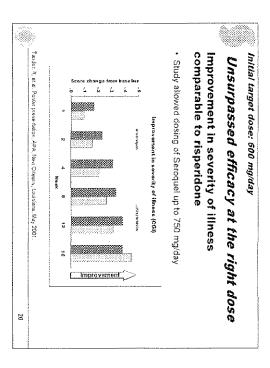
Key communication

The graph and first bullet show the difference between Seroquel and haloperidol in restoring some degree of cognitive

The second bullet points out that cognitive improvement was independent of the other benefits of Seroquel

(improvement in other symptoms, less incidence of EPS)





Data from QUEST support the efficacy of Seroquel compared to risperidone.

## Key communication

Seroquel and risperidone are equally effective in symptom relief.

#### On this page

- The graph, from the QUEST study, shows global improvement
- The same study showed that Seroquel produced less substantial EPS than risperidone

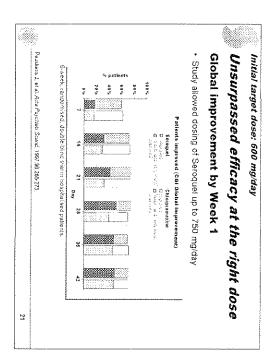
#### About the study

• QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone

Patient Evaluation on Changing Treatment Relative to Usual Medication. CGI: Clinical Global Improvement, EPS: Extrapyramidal symptoms, QUEST: Quetiapine Experience with Safety and Tolerability, SPECTRUM: Seroquel

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The CGI scale is a well-known, well-accepted measurement of overall symptom improvement.

## Key communication

continues to increase throughout treatment. Global improvement-particularly in patients who were "very much" improved-can be seen as early as 1 week and

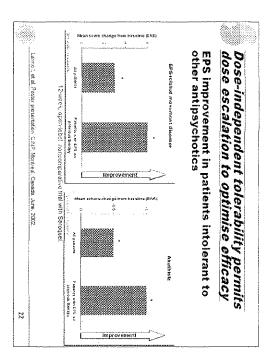
#### On this page

• The graph shows improvement at Day 7, with the ratio of patients "much" and "very much" improved continuing to grow over the 42 days of the study

## About the study

- This was a 6-week study of patients hospitalised with acute exacerbation of schizophrenia
- Tolerability was also evaluated in this study. Fewer patients in the group on Seroquel had parkinsonian symptoms or chlorpromazine akathisia vs those in the chlorpromazine group. Elevated prolactin dropped significantly with Seroquel vs

CGI: Clinical Global Impression



antipsychotics Data from the SPECTRUM study show that a switch to Seroquel can reduce EPS caused by other

## Key communication

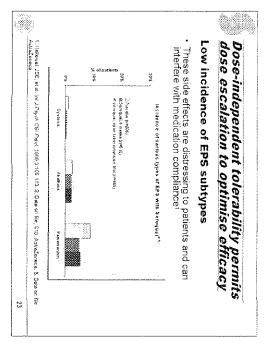
To avoid the EPS caused by other antipsychotics, why not start Seroquel first? On this page

- The graphs, from the SPECTRUM study, show that the incidence of 2 EPS categories-movement disorder and akathisiadecreased in patients switched to Seroquel from other antipsychotics
- Akathisia is a subset of EPS of particular concern to physicians

## About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel
- A total of 506 patients were evaluated for safety
- EPS was measured by the SAS (movement disorders) and BAS (akathisia) scales EPS: Extrapyramidal symptoms. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.

EPS: Extrapyramidal symptoms.



More support for placebo-level EPS, by subtype.

## Key communication

Seroquel shows no more incidence of EPS than placebo when symptoms are broken down by subtype

#### On this page

2 studies confirm the Seroquel safety profile

## About the studies

- Data on File S10 showed that Seroquel showed no difference vs placebo in EPS subtypes across a 75-mg to 150mg dosing range
- (Second DOF info to come from client)

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EPS: Extrapyramidal symptoms.

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1 Ostung DOC, J. Ciell Specielity, 1994 Strought 29-57. 2. Peusiens J. B. J. Psychistry, 1995;165/102-129 3. Oktung prive Prescritting Information 24	And particular And particular	Risperidone and olanzapine demonstrate dose-related EPS
56:712-726 24		strate

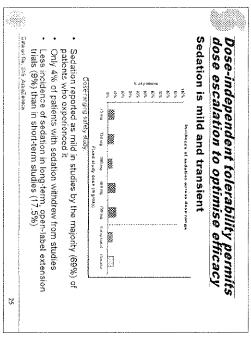
EPS data for risperidone and olanzapine confirm the difference in safety profiles between these atypicals and Seroquel.

## Key communication

Unlike Seroquel, both risperidone and olanzapine show dose-related increases in EPS.

#### On this page

• These graphs expand on the points made in the core detail piece and backup



Reports of the impact of sedation with Seroquel are greatly exaggerated

## Key communication

Sedation associated with Seroquel therapy is transient and mild across the dosing range

#### On this page

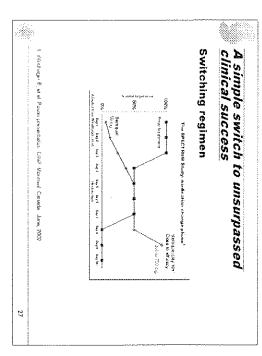
A dosing study shows sedation incidence hardly increases, even at higher doses, and is comparable to haloperidol

## About the studies

 Data on File S19 is from uncontrolled, placebo-controlled, and haloperidol-controlled studies of almost 3,000 patients taking Seroquel

Type II diabetes associated with atypical antipsychotic use Incidence of type II diabetes 20% 15.5% fight 10% 60% 0.0% Clozapine Olanzapine Risperidone Seroquel Cross-sections' study of SCB patients Cross-sections' study of SCB patients

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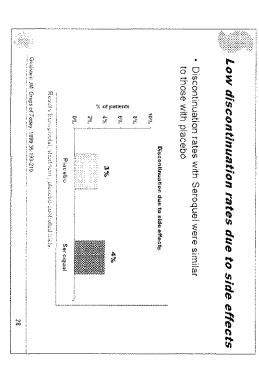
half and increasing Seroquel in a few easy steps. Starting patients who are taking another antipsychotic on Seroquel means simply cutting the current medication in

# Key communication

On which have patients to Seroquel is simple.

• The schematic shows the switch protocol from the SPECTRUM study, in which patients were switched to Seroquel from a variety of other antipsychotics

SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Seroquel tolerability is supported by its low discontinuation rates.

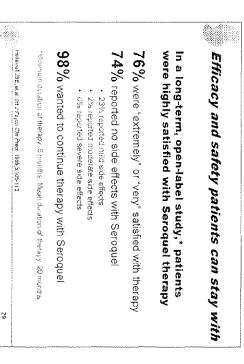
## Key communication

Blacebo, page The percentage of patients stopping therapy with Seroquel due to side effects were essentially the same as with

Simple and compelling evidence of Seroquel tolerability

## About the study

· Pooled data from short-term trials



patients can stay with long-term The efficacy and unique tolerability profile of Seroquel add up to patient satisfaction, providing therapy that

## Key communication

Aptuse 14 genesi in continuing therapy with Seroquel The great majority of patients were highly satisfied with long-term Seroquel efficacy and tolerability. Almost all

• The numbers link patient-reported satisfaction with efficacy and tolerability, with the conclusion that virtually all of them would continue therapy

#### About the study

- 129 patients from 12 countries who had been on Seroquel for at least 6 months and currently in open-label studies were asked to complete a questionnaire about satisfaction with therapy
- Mean treatment duration with Seroquel was 19.9 months, with 38% of patients on treatment for 31 to 42 months
- The most common characteristics patients reported that they liked about Seroquel were lack of side-effects or improvement in side effects caused by other medications
- 96% of patients who expressed a medication preference indicated a preference for Seroquel over previous antipsychotics for both efficacy and tolerability