TEVA PHARMACEUTICAL INDUSTRIES LTD.





Global Innovative Resources

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September 9, 2008
Jerusalem

Teva's Innovative Strategy





- $3 Billion in risk-adjusted revenues by 2012
- Strong growth of Copaxone® and Azilect®
- Building a portfolio that drives growth past 2012
- Leveraging Teva's expertise, capabilities, synergies
- Extending our capabilities into additional focused therapeutic areas



Copaxone®

Multiple Sclerosis Market Dynamics



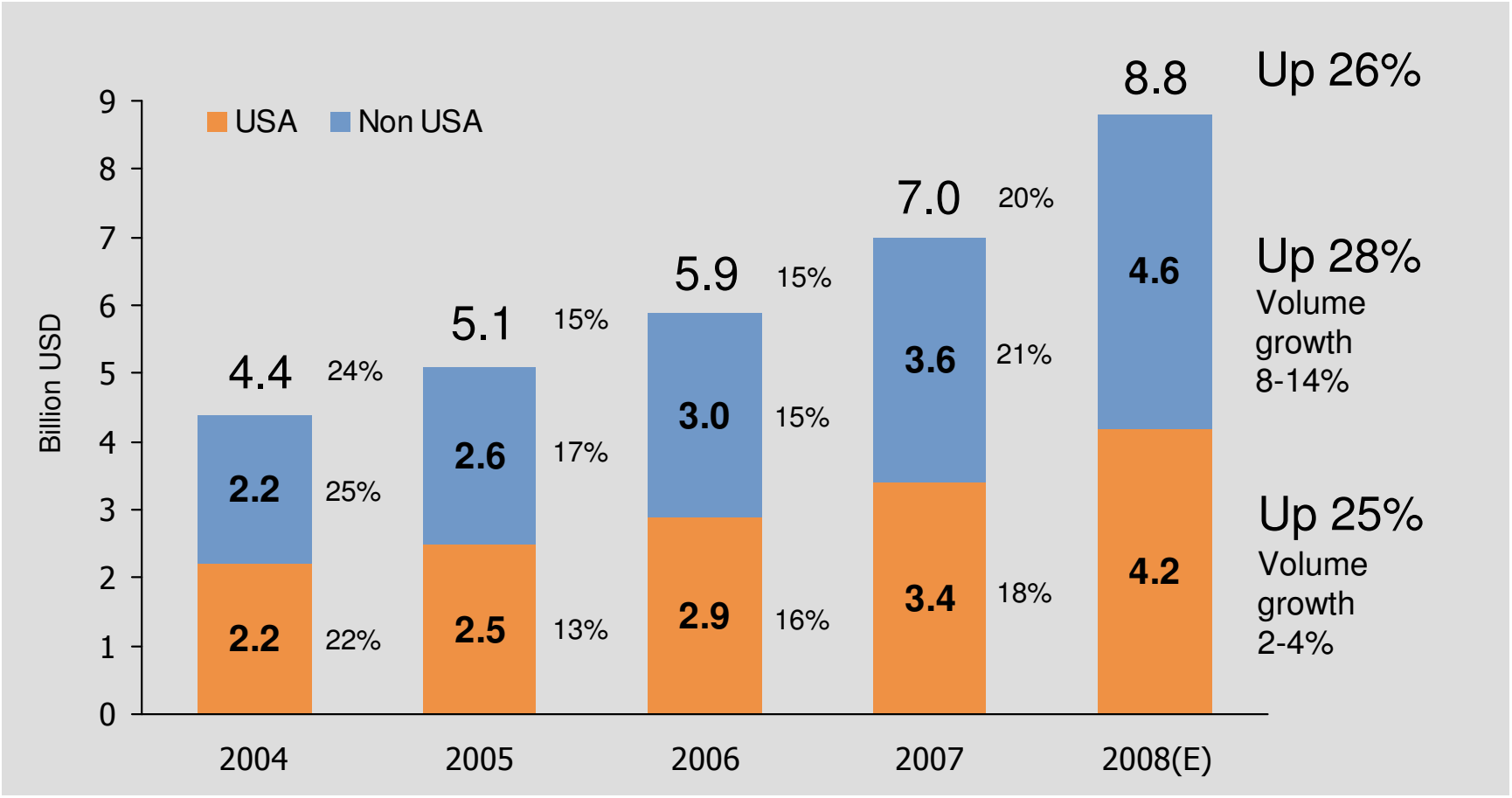


- **Significant June YTD value growth of 30% globally**
  - US: Substantial price increases and slow volume growth
  - Outside US: Higher volume growth than US driven mainly by earlier treatment and patients resuming therapy
- **Copaxone® and Tysabri® increasing their market shares**
- **All INFs are losing market shares (total of 5% decrease in H1)**
- **Availability of ample data from large clinical trials (H2H, PreCISe) with impact on treatment approach**
- **Increased number of clinical trials for new products**

Global MS Market Represents High Growth Rate



In-Market Sales ($ Billion)



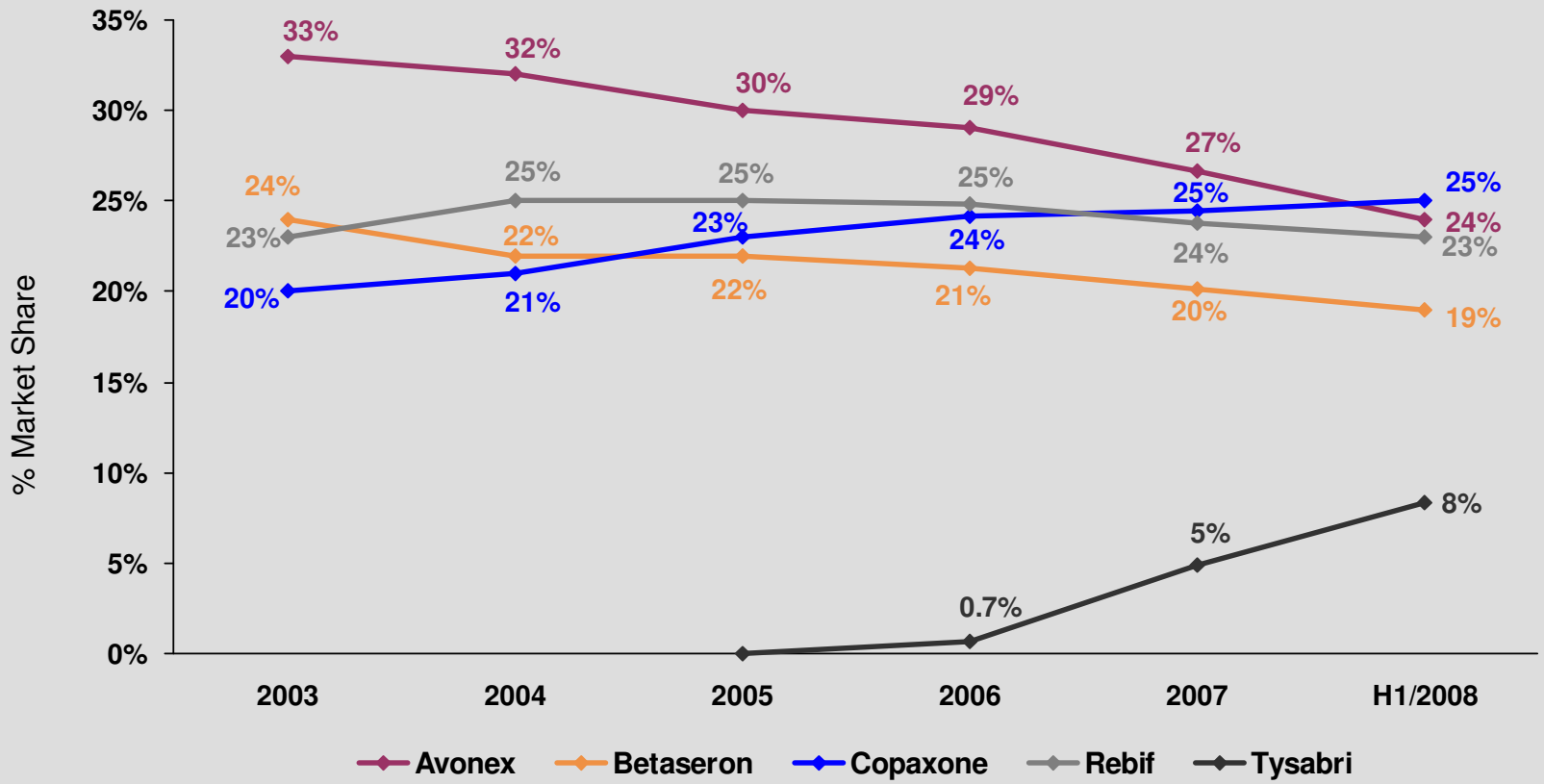
Source: Published companies financial reports and Teva's estimate for 2008

Copaxone®, the Number One Global MS Therapy





Global Market Share (in value)

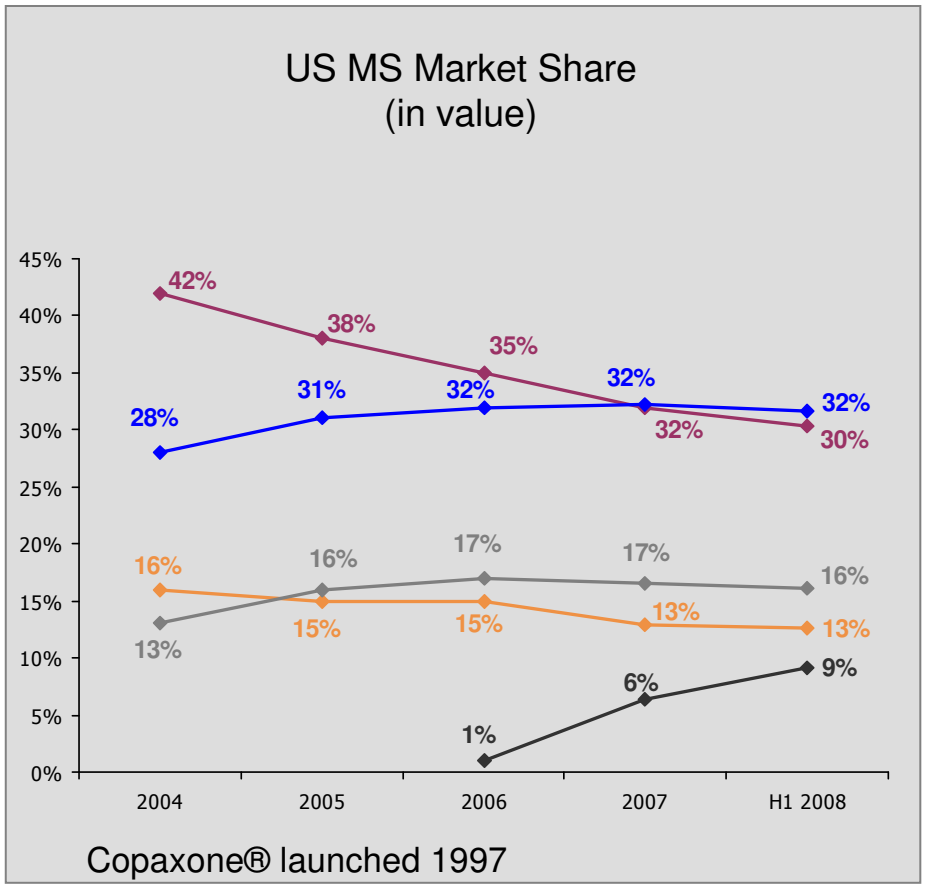


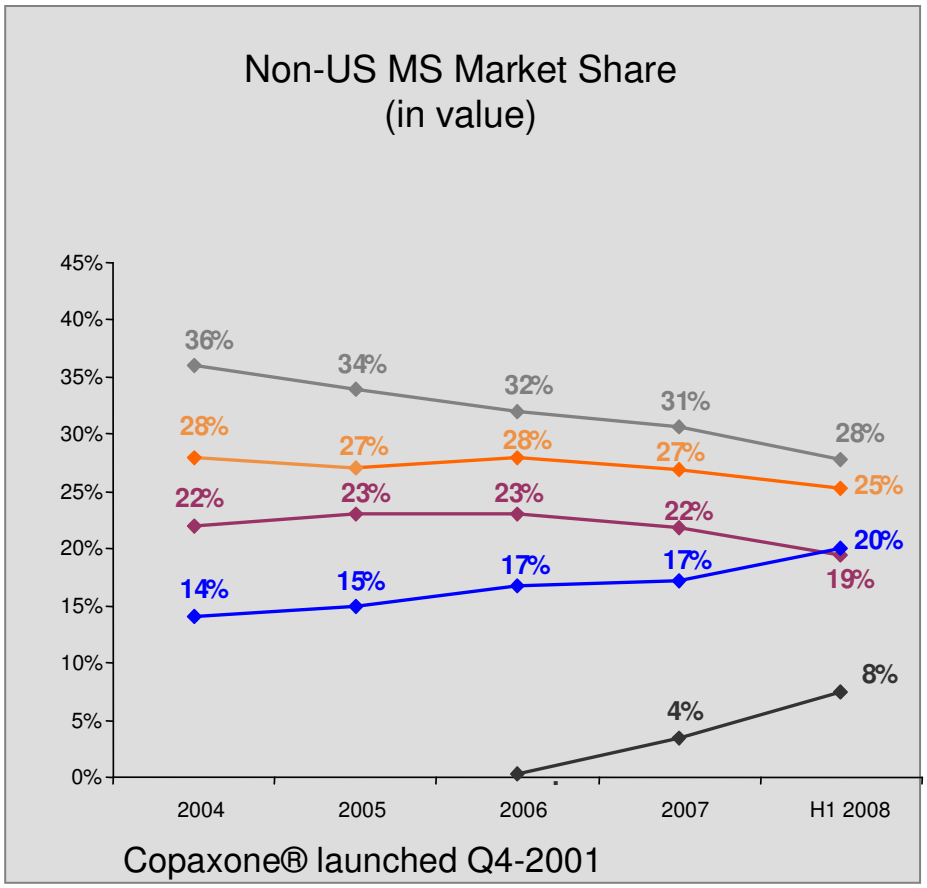
Source: Published companies financial reports

Copaxone® Continues to Increase Market Share Both in the US and Outside the US









Avonex Betaseron Copaxone Rebif Tysabri

Source: Published companies financial reports

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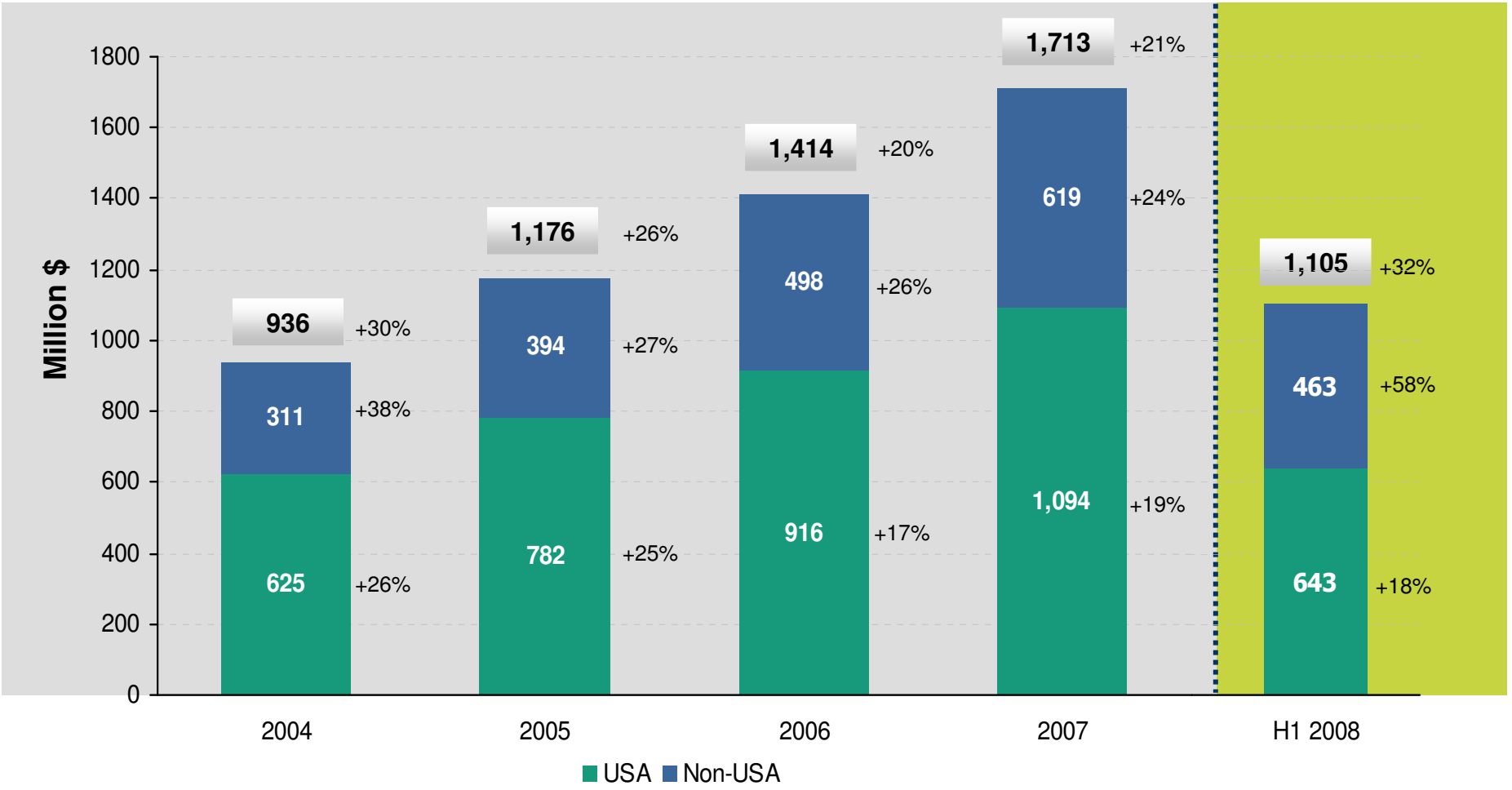
Copaxone®: Highlights of H1 2008 Results





Copaxone® In-Market Sales - Development by Geography

In-Market Sales ($M)



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Copaxone® – Non-US Markets





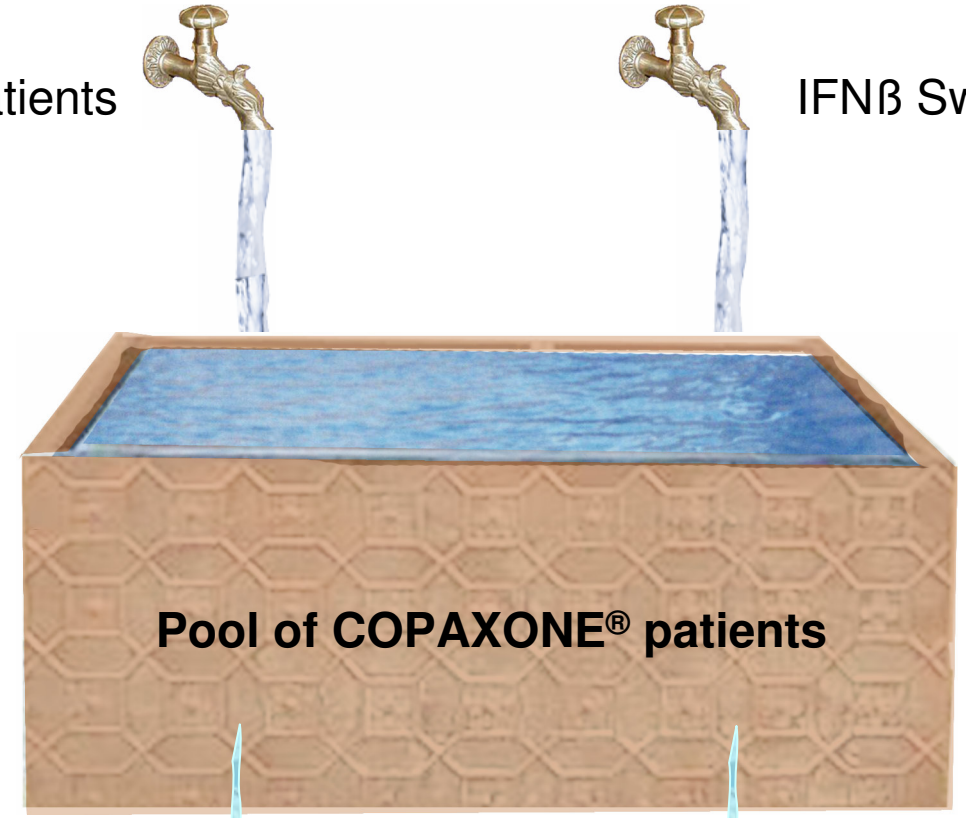
- **Canada –** Copaxone® is leading the market with share of 31.4% and continues to present high growth rate
- **Germany –** Copaxone® ranks #2 with high sales growth, outpacing the market growth and closing the gap with the market leader. Number 1 in naive and switchers patient share
- **France –** Copaxone® ranks #2 with sales growth of over 40%. While Copaxone® is highly used in the hospital market, Avonex® is leading in the retail market
- **UK –** In this conservative market, Copaxone® ranks 1-2 and is presenting substantial growth
- **Italy and Spain –** Although Copaxone® ranks #4, it continues to outpace the market growth while closing the gap with its competitors representing robust growth of over 40%

Dynamics in Copaxone® Growth



Treatment-naïve patients

IFNß Switchers



Switching to IFNß

Switching to Tysabri®

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Achieving a Sustained Growth in Copaxone®-treated Patients





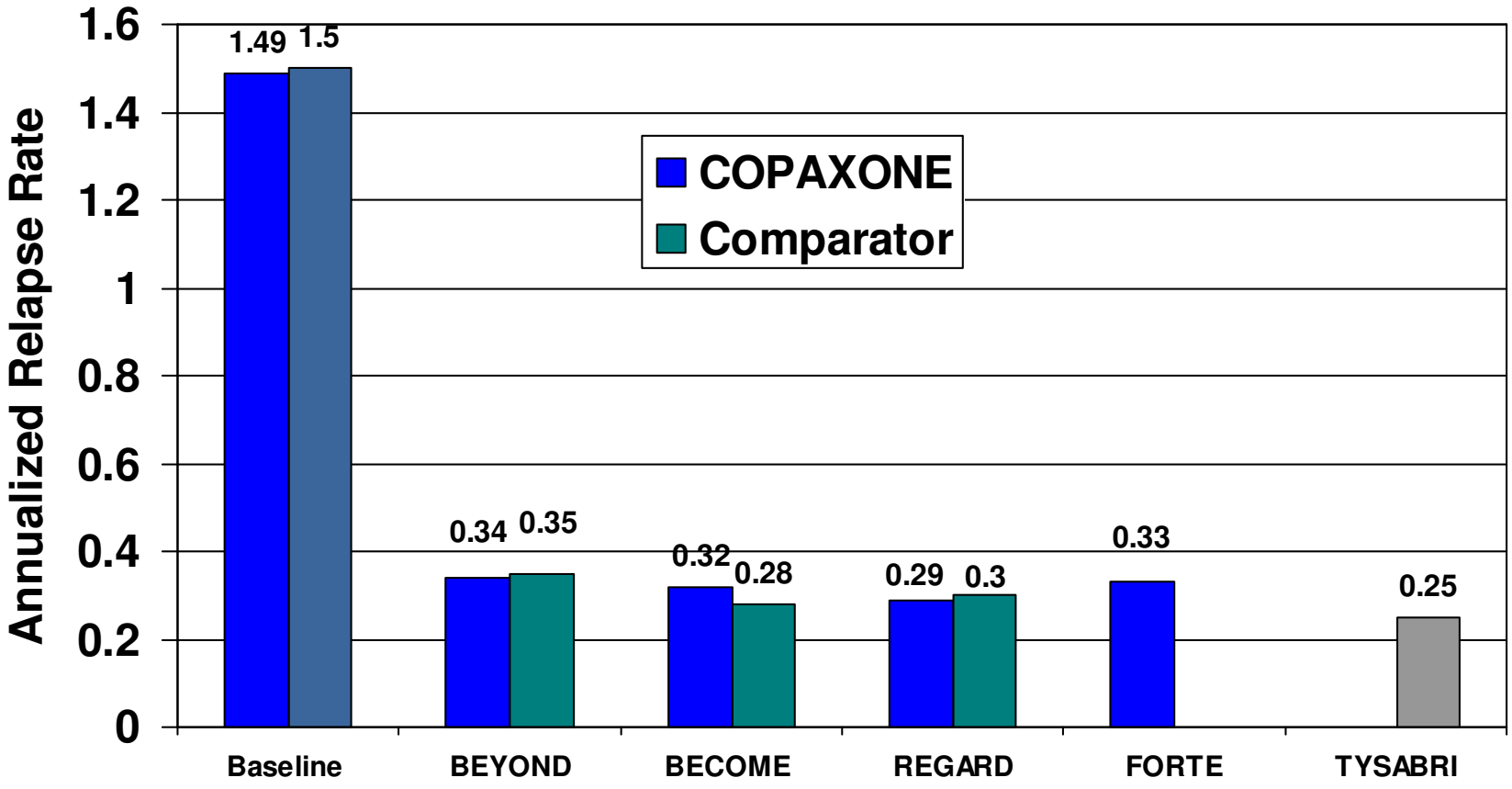
Increases Patients' Pool – 1st choice therapy in both naïve and INF switching patients

- Treatment-naïve patients
  - A trend for early diagnosis and treatment
  - A proven record of increasing market share at the expense of INFs
  - Extension of indication to include CIS patients
- Most IFNs Patients continue to switch to Copaxone®
  - Results from short term H2H studies on relapse rate confirm that Copaxone® is as potent as other DMTs, including Tysabri®
  - Low relapse rate (0.33) achieved in the FORTE trial further support switching
  - Demonstrated efficacy and safety after switching to Copaxone®
  - Unmatched long term efficacy and safety

Trends Across Clinical Trials: Annualized Relapse Rate







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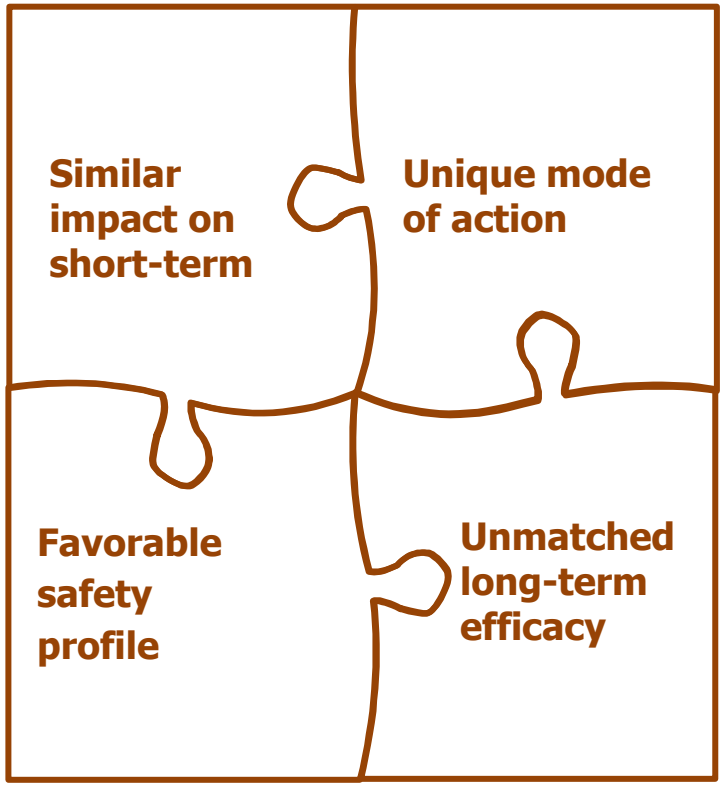
Future Copaxone® Driven by a Unique Differentiation from Competitors





Copaxone® potency is comparable to the competition in short term disease activity for both CIS and RRMS patients

Copaxone® offers a better safety profile in the short & long term



Only Copaxone® can address all aspects of MS:

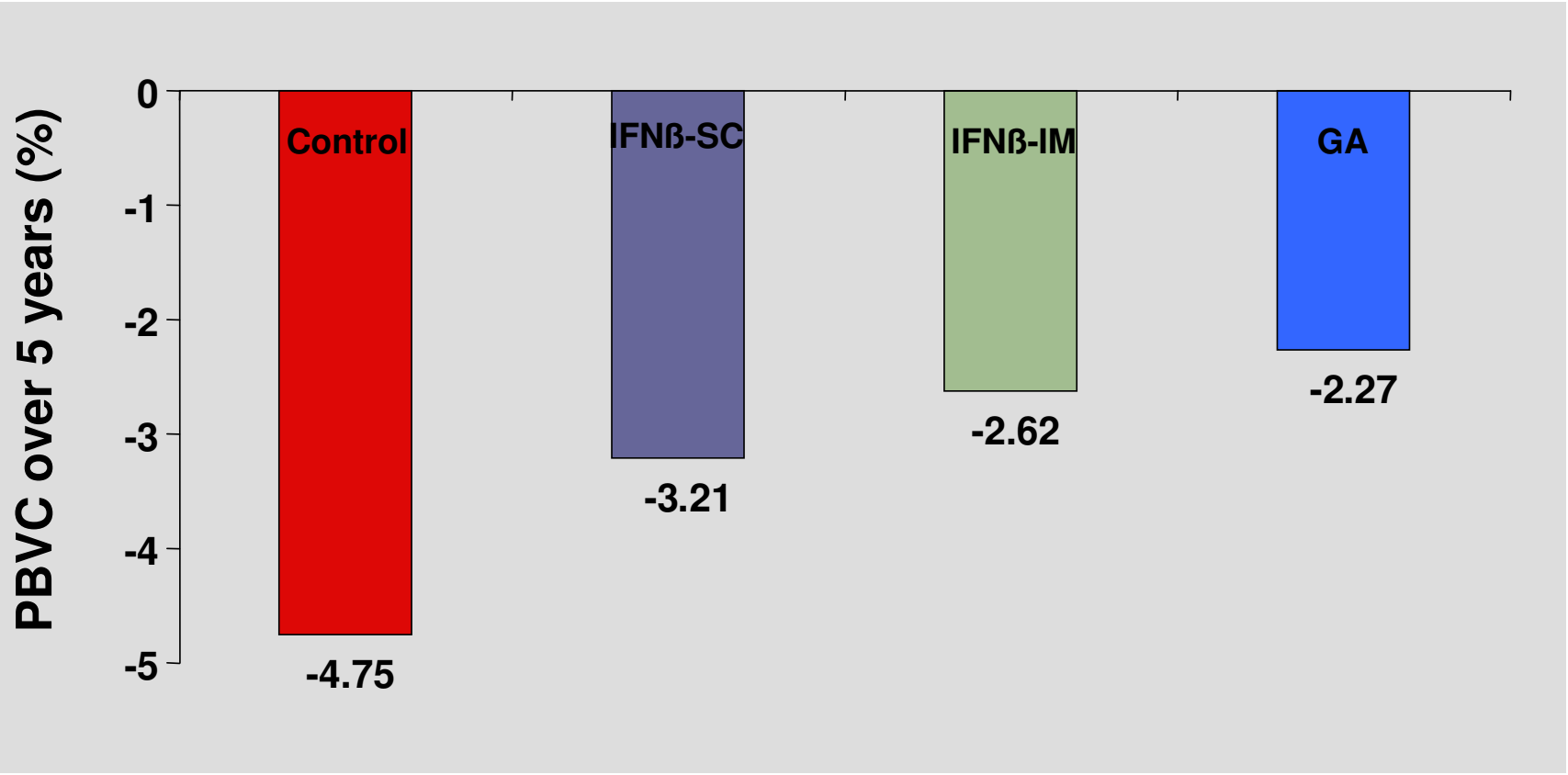
- Regulates inflammation
- Slows neurodegeneration
- Promotes axonal repair

Only Copaxone® demonstrated long term efficacy and safety in a continued prospective, long-term study

Differential Effect of GA on Neurodegeneration



Brain Atrophy in Early and Mildly Affected RRMS: Results of a five-year imaging study



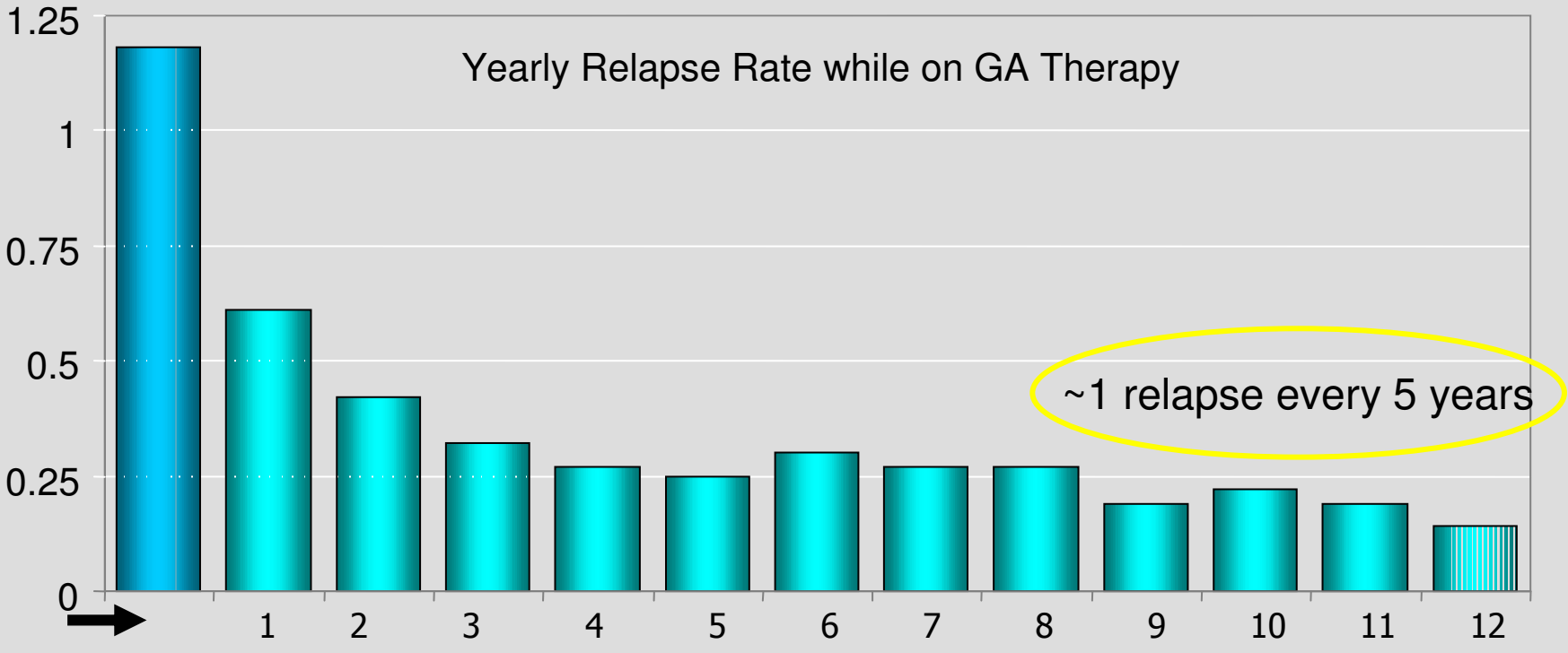
Khan O, et al. Presented at: 23rd Congress of the European Committee for Treatment and Research in Multiple Sclerosis; October 11-14, 2007; Prague, Czech Republic.

Lasting efficacy and safety confirmed for over 10 years





- Only Copaxone® has long-term, continuous-use, prospective studies
- The majority of patients on long-term Copaxone® therapy remains **clinically stable or improved**
- 92% of patients still **walking without assistance after 10 years**
- Unsurpassed safety and tolerability



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Copaxone® – Summary





- Copaxone® will continue to lead the global MS market in this decade
- Copaxone® reached sales of $1.1 Billion in H1-2008 representing a 32% growth over H1-2007, adding in-market sales of $268 Million in 6 months
- Copaxone®'s continued growth will be driven by:
  - Increased share in treatment-naïve and early MS patients
  - Continued Increase in IFNs switching patients supported by a unique differentiation
- Copaxone® has growth opportunities in emerging markets – Latin America, CEE and some Western EU countries.
- Copaxone®'s unique clinical benefits and safety profile provide a major advantage in the future competitive arena
- **Teva** is committed to leadership in MS by a robust pipeline of improved and new therapies



Why a Generic Copaxone® Presents Unique Challenges

Copaxone®





- It is impossible to fully characterize qualitatively and quantitatively the exact composition of Copaxone®
- Although Teva is constantly raising the level of scientific understanding through state of the art methods, GA is a complex product that may never be fully characterized
- In most ways, GA should be considered a biologic because of its mechanism of action and the chemistry of the mixture of substances
- Any change in the peptide sequence or attributes, results in a product with unknown efficacy and safety, an NCE

Copaxone®





- Because GA can not be fully characterized and because blood levels are not indicative of clinical effect, traditional bioequivalence studies are not meaningful
- A clinical study should be required to determine clinical equivalence
- New glatiramoids should also be considered new chemical entities
- Immunogenicity, toxicity profile, and clinical efficacy should be established
- A clinical trial with relapse rate as the endpoint is the only meaningful benchmark to establish therapeutic equivalence with Teva's GA



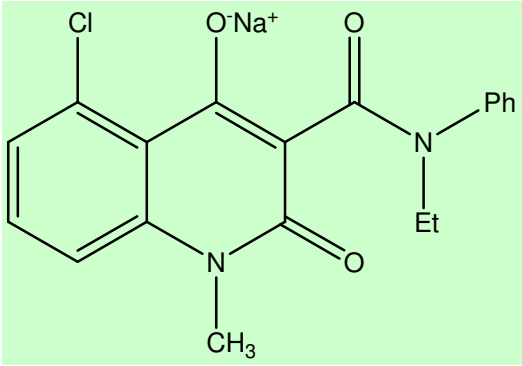
Next Generation MS Projects – Laquinimod for RRMS

Laquinimod





A novel synthetic compound licensed from Active Biotech (2004): a quinoline-3-carboxamide derivative



5-chloro-1, 2 – dihydro-N-ethyl-4-hydroxy-1-methyl-2-oxo-N-phenyl-3-quinolinecarboxamide sodium salt

- **Indication – Relapsing Remitting MS**
- **Route of administration – oral**
- **Development stage – two phase III studies ongoing**

Laquinimod: Key Characteristics





- Once daily, oral administration 0.6 mg/day
- Immunomodulator, NOT AN IMMUNOSUPPRESSOR
- Favorable long-term safety profile
- Excellent tolerability
- Early, sustained & reproducible effects on MRI activity
- 60% reduction in median number of Gd-T1 Lesions
- Trend of 33% reduction in relapses in a Phase II trial

Results from the First Phase II Study (AB)





- The 0.1mg/d dose did not show any meaningful/significant effect
- The 0.3mg dose showed a clear biological activity on the evolution of inflammatory lesions in this cohort
- With an encouraging safety profile, it was decided to perform an additional Phase II study, with a higher dose

Polman C, et al. *Neurology*. 2005;64:987-991

Teva's Phase IIb STUDY (LAQ/5062)





Study Design

- Double-blind, Placebo controlled study
- Duration – 36 weeks
- Patient population – RRMS, with ≥1 enhancing lesions in screening MRI scan
  - Laquinimod 0.6mg – 106 patients
  - Laquinimod 0.3mg – 98 patients
  - Placebo – 102 patients
- MRI (T1/T2) performed at weeks 12, 16, 20, 24, 28, 32 and 36
- Safety assessment performed every 4 weeks

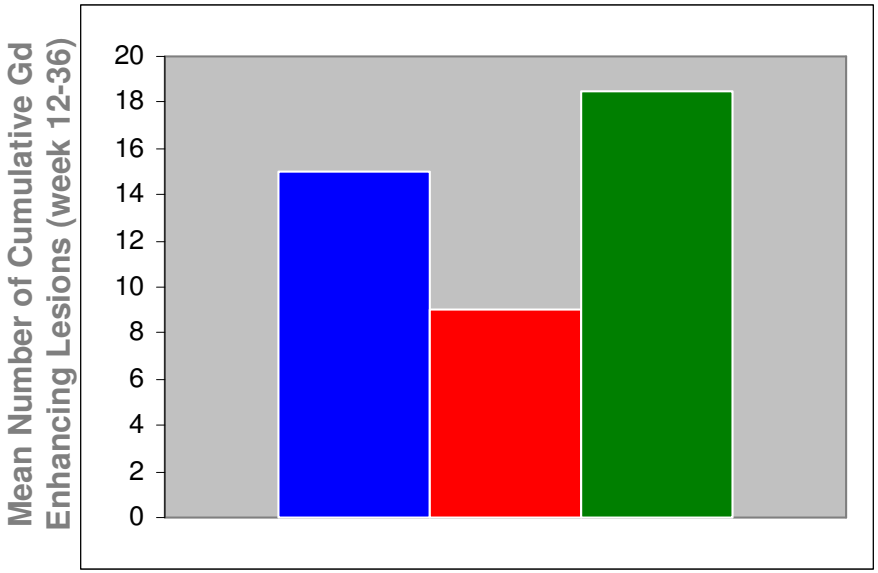
Comi, et al (LAQ/5062 Study Group). *Lancet*. 2008;371:2085-92.

Laquinimod 0.6 mg Significantly Reduced T1 Gd-Enhancing Lesions

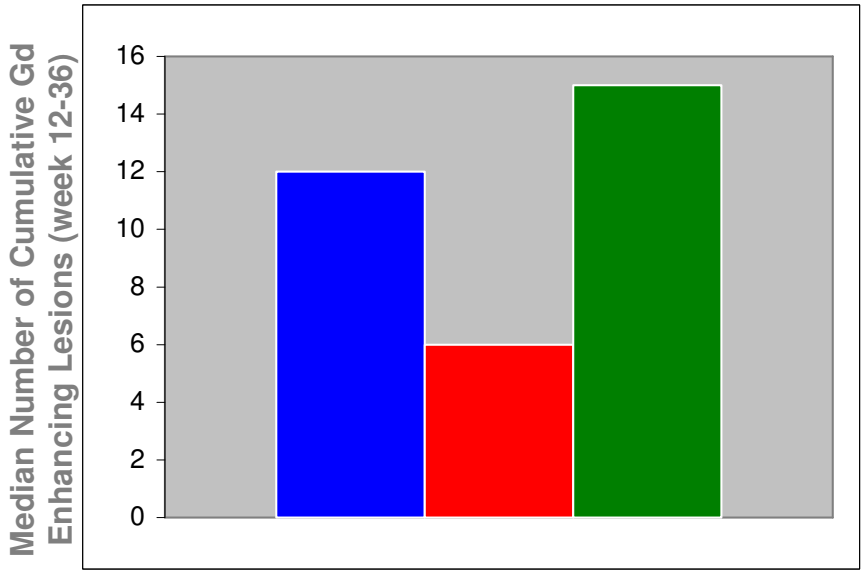




51% Reduction (Week 12-36) (Mean*) p < 0.0001



60% Reduction (Week 12-36) (Median) p=0.01



* Adjusted means

- 0.3 mg Laquinimod
- 0.6 mg Laquinimod
- Placebo

Comi, et al (LAQ/5062 Study Group). *Lancet*. 2008;371:2085-92.

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Effects of Laquinimod on Additional MRI Measures (0.6 mg dose)





Outcome Measure	% Reduction From Placebo	
	Mean	Median†
Cum. Number of Gd-T1 Lesions (week 12-36)	51% (p=0.0001)	60% (p=0.01)
Cum. Number of Gd-T1 Lesions (week 24-36)	40% (p=0.0048)	55% (p=0.03)
Cum. Number of New T2 Lesions (week 12-36)	50% (p<0.0001)	55% (p=0.001)
Cum. Number of New T2 Lesions (week 24-36)	44% (p=0.0013)	40% (p=0.01)
Cum. Number of New T1 Hypointense Lesions (week 24-36)	50% (p=0.0064)	--
Deterioration in Brain Atrophy (week 0-36)	30% (p=0.07)*	--

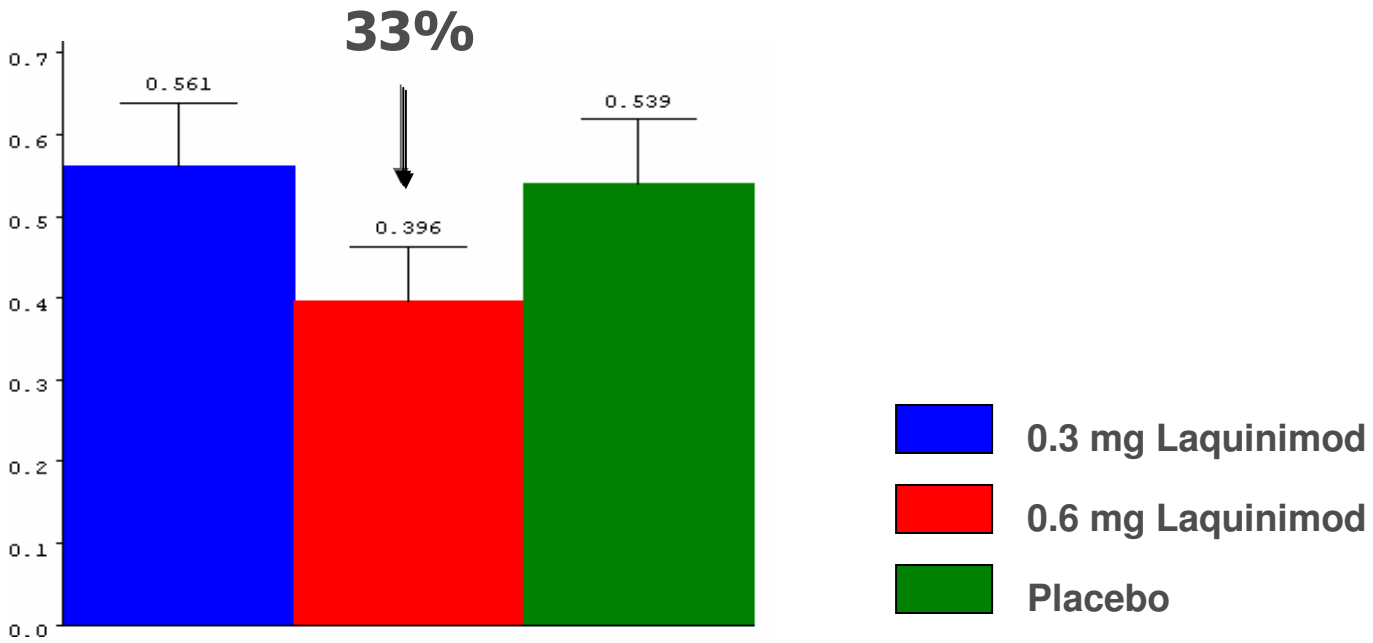
* Adjusted to baseline T2-lesion volume; SIENNA: 0.6mg: -0.4; Placebo: -0.58
† Wilcoxon rank test

Comi, et al (LAQ/5062 Study Group). *Lancet*. 2008;371:2085-92.

Laquinimod's Effect on Relapse Rate



Annualized Relapse Rate



- Trend (p=0.09) toward reduction of annualized relapse rate
- Study was not powered to detect a statistical effect on relapse rate

Comi, et al (LAQ/5062 Study Group). *Lancet*. 2008;371:2085-92.

Laquinimod is Safe and Well Tolerated





- Similar drop out rate to placebo
- No effect on vital signs
- No effect on ECG
- No specific pattern of adverse events

Liver Enzyme Elevation:

- Reversible
- Most normalized while on Laqunimod
- No signs of liver damage/failure
- No concomitant bilirubinemia

LAQ/5062 Study	Elevations to potentially Clinically Significant Levels		
	Placebo (n=102)	0.3mg (n=98)	0.6mg (n=106)
ALT (x3)	2 (1.9%)	2 (2.0%)	8 (7.5%)
AST (x3)	3 (2.9%)	1 (0.9%)	1 (0.9%)
Bilirubin (x2)	3 (2.9%)	0	0

Comi, et al (LAQ/5062 Study Group). *Lancet*. 2008;371:2085-92.

Laquinimod – Summary





- In LAQ/5062 study, an oral, once-daily dose of Laquinimod 0.6mg has shown:
  - A robust, consistent and early effect on MRI activity in RRMS patients
  - A trend in reducing the number of relapses (the study was powered to detect an effect on MRI activity)
  - A trend in slowing the progression of brain atrophy
- The effect of Laquinimod 0.6mg on MRI activity is sustained and reproducible in the extension phase of the study
- Laquinimod 0.6mg is safe and tolerable
- Prolonged exposure in the extension study shows:
  - No emergence of new safety signals
  - No cases of myocardial ischemia/infarction or pleuritis/pericarditis
  - Decrease in the incidence rate of liver enzyme elevations



Next Generation MS Projects – ATL/TV-1102 for RRMS

ATL/TV-1102





- TV-1102 was licensed in Feb 08 from ATL, an Australian based company while a Phase IIa in RR-MS patients was ongoing.
- ATL originally licensed the product from ISIS pharmaceuticals an US based company whose expertise is development of antisense drugs
- TV-1102 is a 2nd generation novel anti-sense drug for the treatment of multiple-sclerosis
- Antisense drugs block the production of disease-causing proteins by interacting with their DNA (genetic code)
- Antisense is a powerful and productive new basis for drug discovery
- It is a small synthetic molecule, 20 oligonucleotides long
- TV-1102 is targeted to inhibit VLA-4 expression

VLA-4 is a Validated Target for the Treatment in MS





- VLA-4 is a key adhesion molecule which plays important roles in mediating leukocyte trafficking to peripheral organ, such as the brain, by binding to its endothelial cell ligands VCAM-1, JAM-2 and extracellular matrix protein Fibronectin
- VLA-4 integrin molecule expressed at high level on all circulating leukocytes
- VLA-4 inhibition is a validated target in MS (Tysabri®)
- However, Unlike certain monoclonal antibody drugs, antisense drugs have not been associated with JC virus activation or PML. To date there are no indications to suggest that ATL/TV1102 may cause PML

Phase IIa Study Characteristics

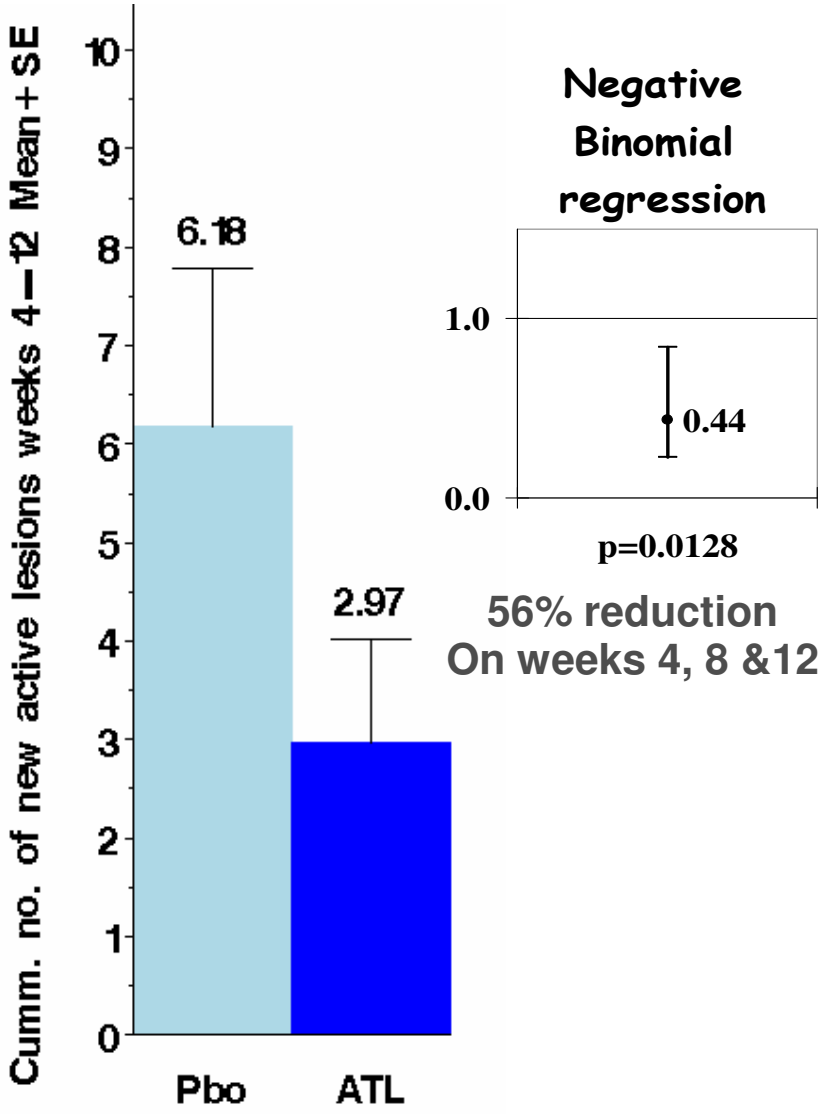


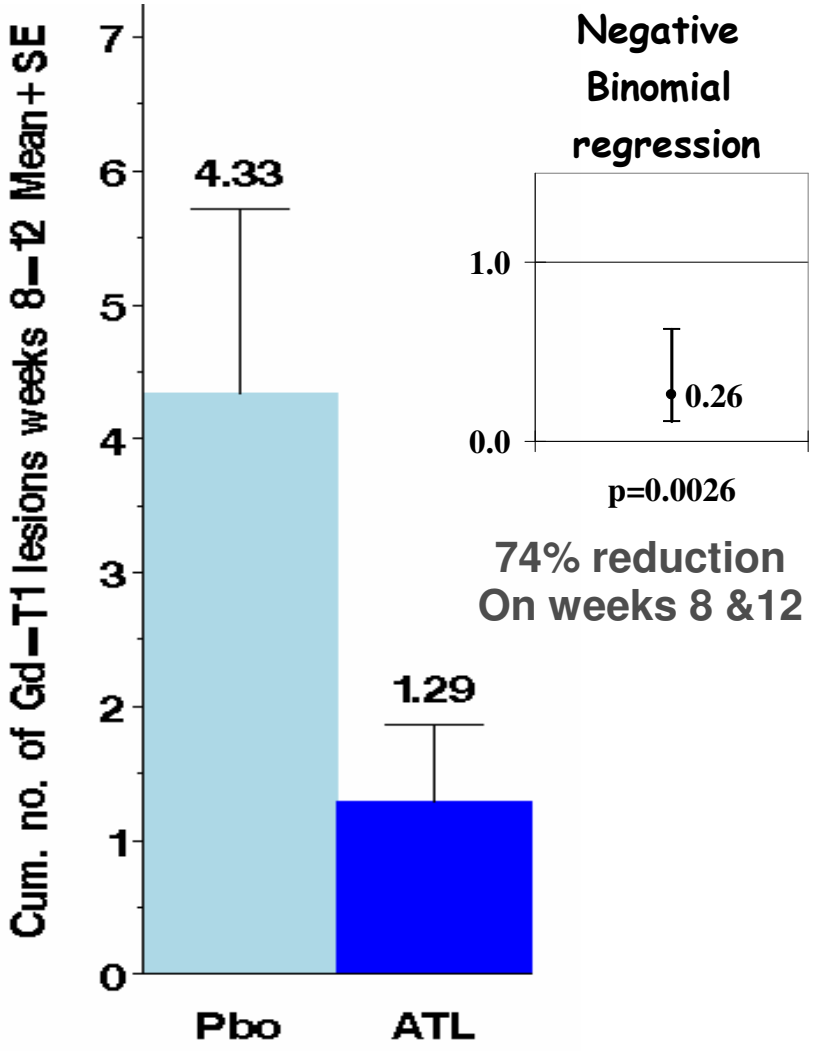


No. of Patients	77 Patients randomized (80 patients were planned) The sample size assumption was 85% power to detect an effect of 66.7% over placebo
Countries	Germany, Slovakia, Romania, Bulgaria, Czech Republic, Poland
No. of centers	20 centers
Study PIs	Dr Limmroth – Köln MRI AC – Prof Barkhof - Amsterdam
Study design	Patients administered three induction doses of 200mg or placebo on days 1,4,7 and then 200 mg or placebo twice a week for seven more weeks Assessments at weeks 4,8 (during treatment) and weeks 12,16 (post-treatment) PEP - The cumulative number of new active lesions on weeks 4, 8, and 12

TV-1102 Reduced The Cumulative Number of New Active Lesions







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ATL/TV-1102 – Summary





- The efficacy of TV-1102 based on MRI in the Phase II study was remarkable
- Results were comparable to those observed by Tysabri® in their first Phase II study (Neurology 1999)
- Potentially attributable adverse events included injection site reactions which were mild to moderate and thrombocytopenia
- Thrombocytopenia was reversible after treatment interruption returning to within normal ranges and was not accompanied with any clinical consequences
- Based on the effect seen in week 12 (4 weeks following stop of treatment) we have a basis to believe that reduction of dosing frequency is feasible
- Reducing the frequency of administration may potentially reduce the safety issues observed



Other MS Products in Development

The Future of MS Therapies





Naive patients → **First-line therapies** → **Copaxone®**, **IFNs**

Consistent effect on relapses and MRI

Further optimisation of dose and frequency

Effect on long-term disability

Potential to further enhance efficacy and ease of use

Emerging therapies and strategies

Oral treatments
Cladribine
FTY 720
Teriflunomide
Laquinimod
BG-12

Cytotoxic agents
Mitoxantrone

Monoclonal Antibodies
Natalizumab
Daclizumab
Rituxan
Alemtuzumab
Daclizumab

Antisense Therapies
ATL1102

Ag-specific Therapies
MBP 8298

The Future of MS Therapies: Safety Issues





- Monoclonal antibodies (Alemtuzumab anti CD52; Campath-1H and Natalizumab anti VLA-4) – can be associated with specific side-effects, e.g. PML, Graves' disease, ITP
- FTY720 – Macular edema (10 cases in phase III) and 7/250 skin malignancies in phase II
- Cardiotoxicity with mitoxantrone
- Therapy-related acute leukaemia is a potential risk with some cytotoxic combinations
- Exacerbation of MS disease activity as seen with TNF-α antagonism
- Long term safety and efficacy of Copaxone® will be preferred considering the safety concerns with the future drugs



Azilect®

Parkinson's Market Dynamic

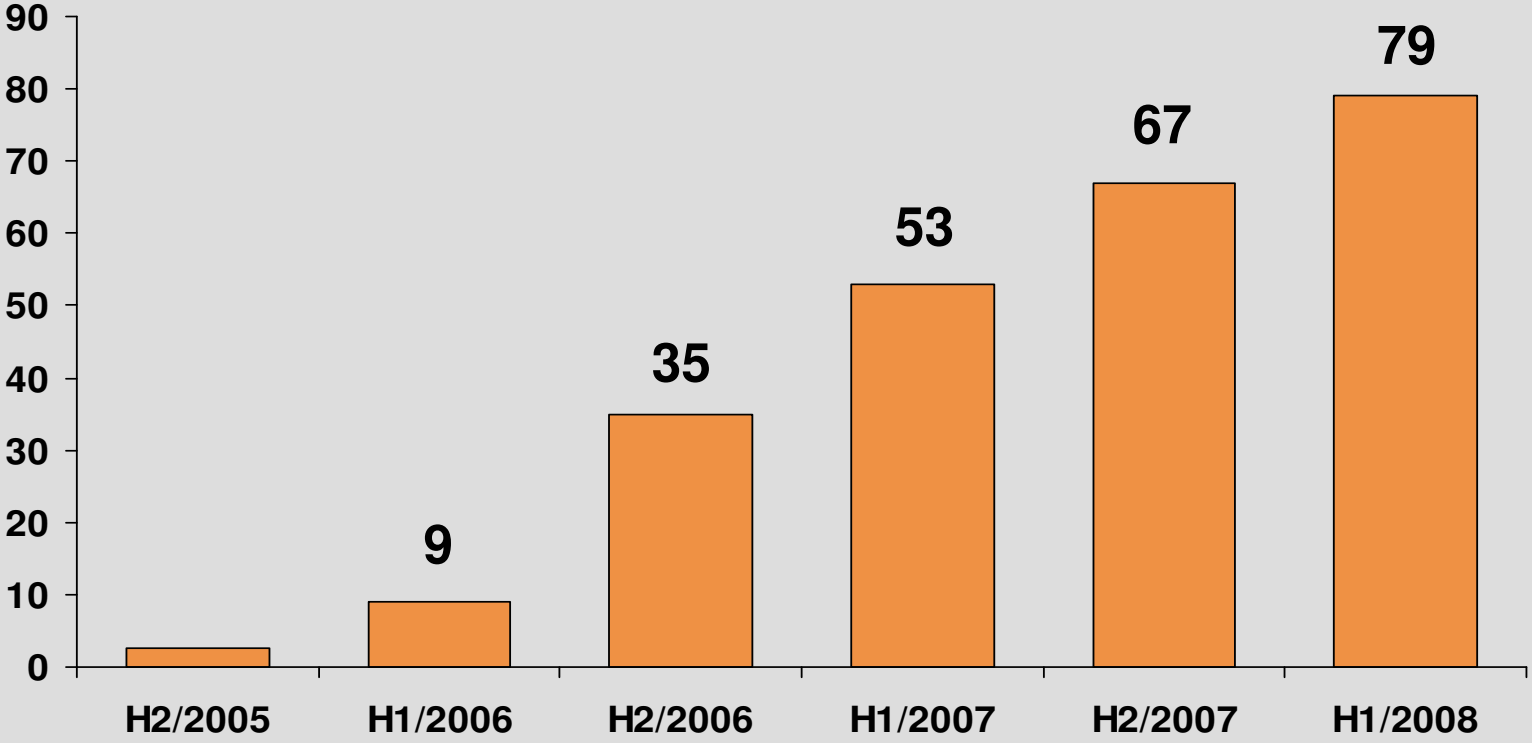




- Global PD market size 2007 – $3.3 billion
- Global PD market est. growth in '08: 2- 4% in patients, 6-8 % value
- Main growth drivers - earlier treatment and expensive drugs
- Market split ~50%-50% monotherapy and adjunct therapy
- Leading PD Products become generic (Requip IR & Mirapex)
- ReQuip once daily introduced in the US during 2008
- Continuing trends of earlier diagnosis and treatment in PD, and search for biomarkers
- Azilect® first product to demonstrate effect on disease progression

Azilect® In-Market Sales ($ Millions)





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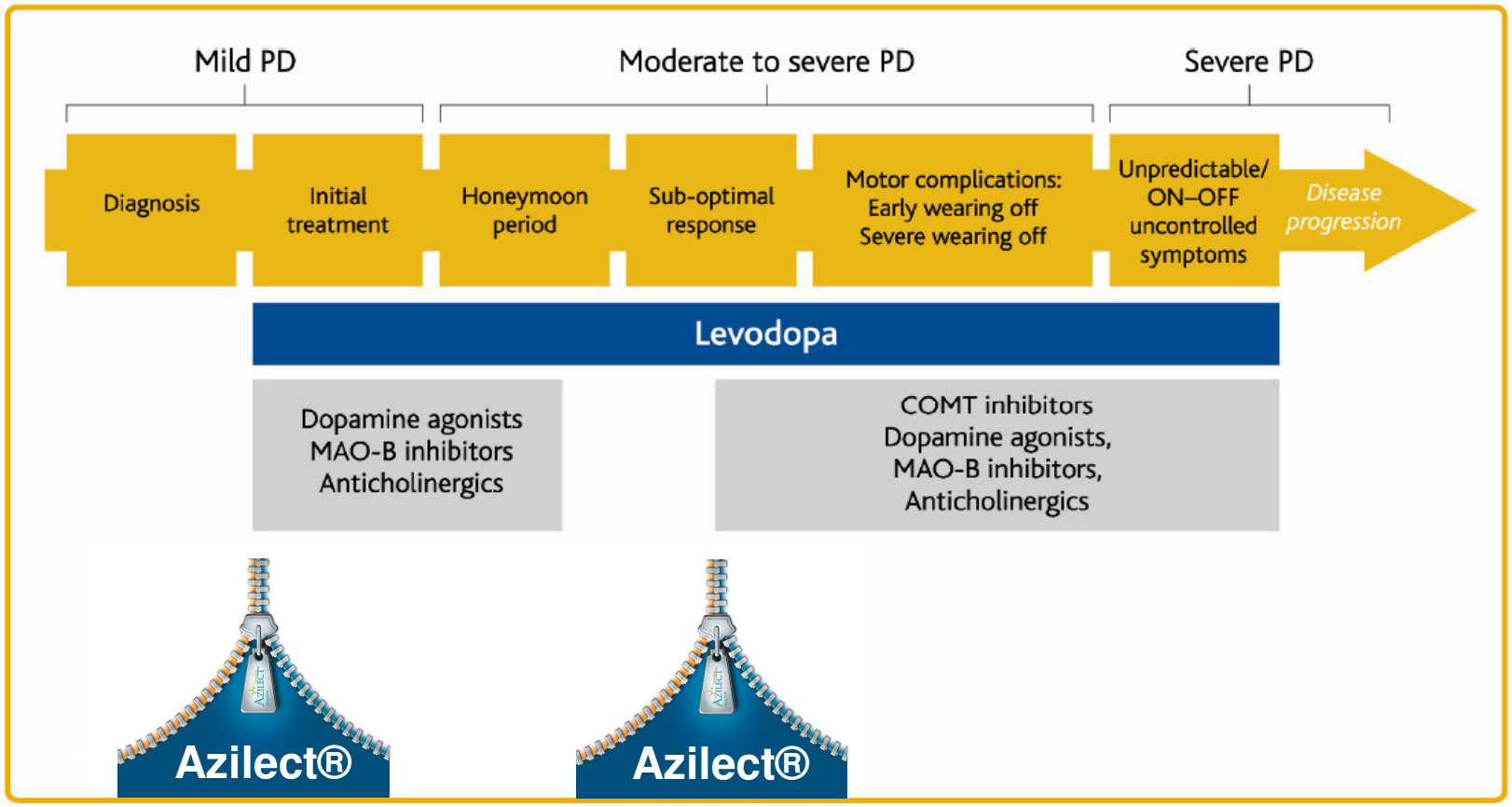
Azilect® drug of choice for all PD disease stages







Azilect® Growth Drivers





- ADAGIO results will re-position the product from symptomatic treatment in mono and adjunct to disease modifying agent fulfilling PD unmet needs
- PD early diagnosis & treatment trend will make Azilect® drug of choice for all disease stages
- Inclusion of ADAGIO results in labeling
- Once daily tablet, no titration and excellent tolerability
- Strong EU penetration with estimated value market share of 5.5%
- Increased value proposition to payors and patients
- Expand to new markets in the short term (France, Russia, Brazil) and in the long term – Japan



ADAGIO

ADAGIO: Attenuation of Disease progression with Azilect® GIven Once-daily



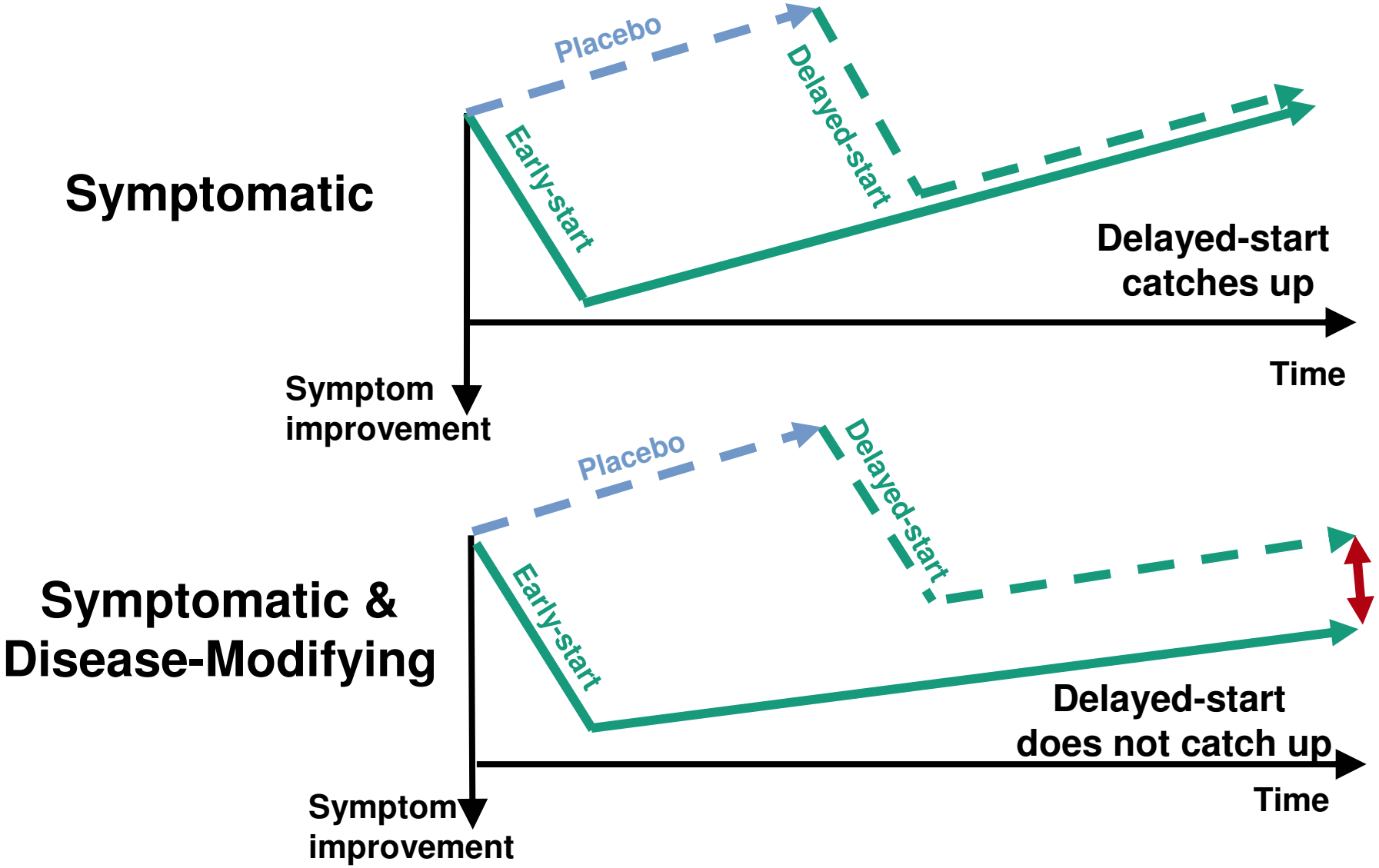


- Background: Rasagiline is a MAO-B inhibitor containing a propargylamine moiety
  - Approved for symptomatic treatment of Parkinson's disease
  - Shows neuroprotective effects *in vitro* and *in vivo*
- Objective: To assess rasagiline as a disease modifying therapy in Parkinson's disease
- Design: 72-week (18-month) delayed-start
- Recruitment: 1,176 early untreated PD patients
  - 129 centres, 14 countries

Olanow et al. Mov Disord. 2008. In press.

Delayed Start Design –
Symptomatic vs. disease-modifying effect





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ADAGIO Eligibility



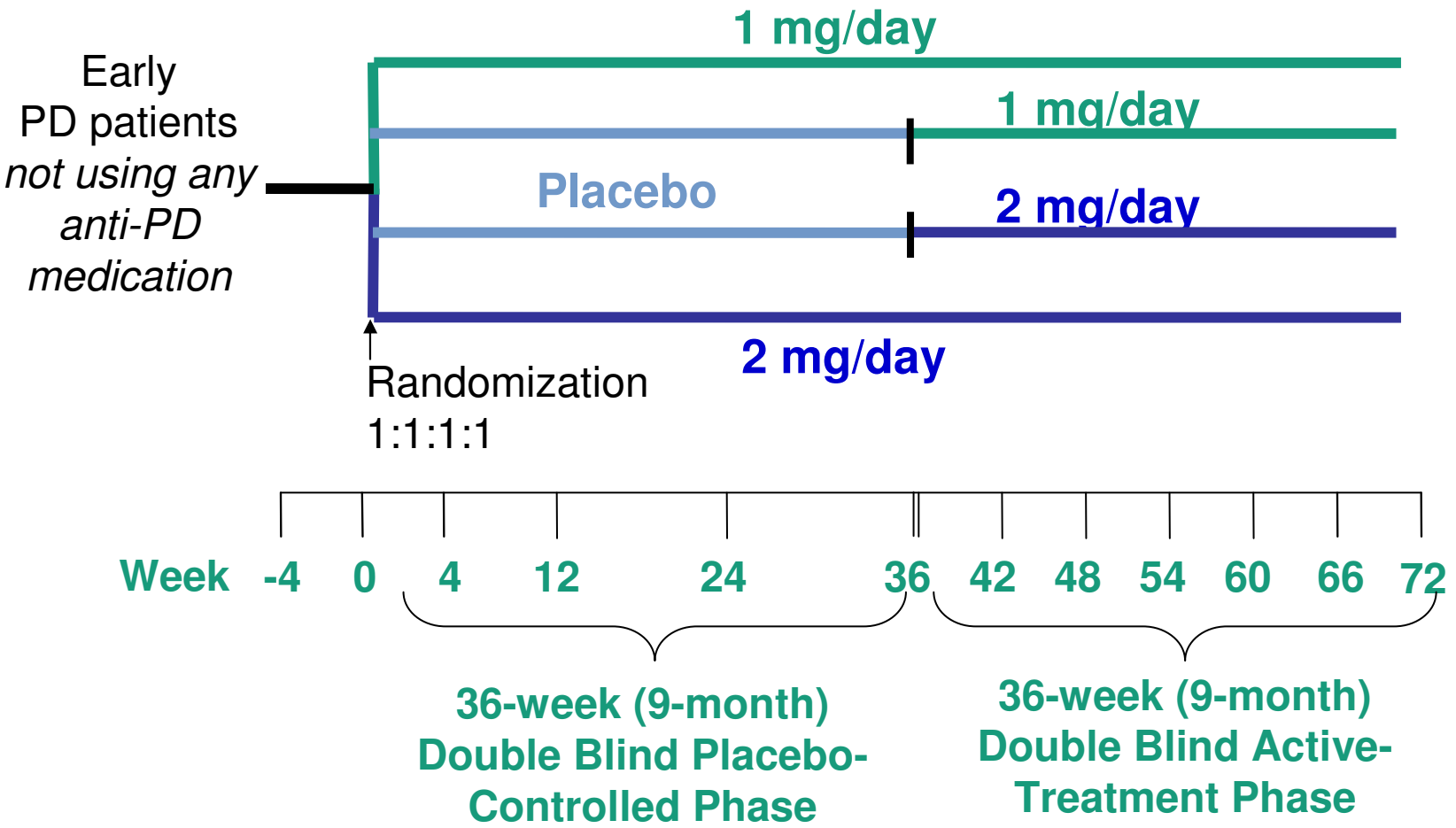


- Patients
  - Men and women 30–80 years of age
- Inclusion Criteria
  - Early idiopathic PD judged not to need symptomatic therapy for >9 months
  - Diagnosis of PD ≤1.5 years before enrollment
  - Hoehn & Yahr stage <3
- Exclusion Criteria
  - Patients with atypical or secondary parkinsonism were excluded
  - Previous use of antiparkinsonian agents for >3 weeks not permitted
  - Unstable medical conditions

Olanow et al. Mov Disord. 2008. In press.

ADAGIO Study Design





Primary endpoint based on Total-UPDRS

Olanow et al. Mov Disord. 2008. In press.

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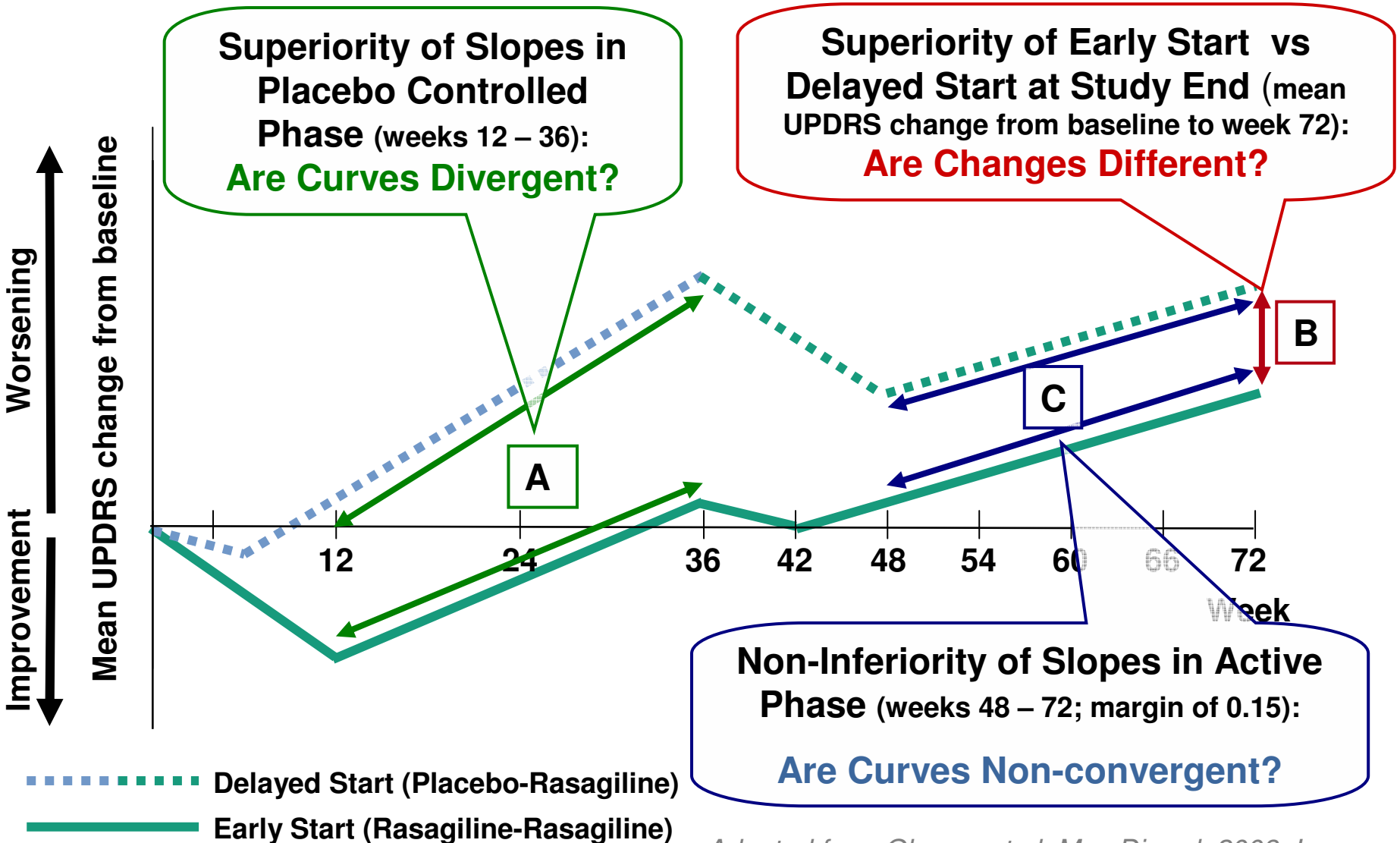
Schematic to Illustrate the ADAGIO Principal Statistical Analyses: 3 Hierarchical Steps





Adapted from Olanow et al. Mov Disord. 2008. In press.

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ADAGIO Baseline Characteristics





Patients randomized (n)	1176
Male patients (n, %)	718 (61.1%)
Age, years (mean, SD)	62.2 (9.6)
PD duration, months (mean, SD)	4.5 (4.6)
UPDRS total score (mean, SD)	20.4 (8.5)
UPDRS motor score (mean, SD)	14.2 (6.4)
Modified Hoehn & Yahr (mean, SD)	1.5 (0.5)

Olanow et al. Mov Disord. 2008. In press.

ADAGIO Results: Primary Analyses (1 mg/day)



- Analysis A: Superiority of Slopes in Placebo Controlled Phase, Weeks 12 – 36
  - $Slope_{(Rasagiline)} - Slope_{(Placebo)} = -0.05$ (p=0.0133; 95%CI: -0.08,-0.01)
  - **Curves are Diverging**
- Analysis B: Superiority of Mean Change in UPDRS Scores at Week 72)
  - $Early\text{-}Start_{(Week\ 72)} - Delayed\text{-}Start_{(Week\ 72)} = -1.7$ (p=0.025; 95%CI: -3.15,-0.21)
  - **Changes are Different**
- Analysis C: Non-Inferiority of Slopes in Active Phase, Weeks 48 – 72; margin of 0.15
  - $Slope_{(Early\ Start)} - Slope_{(Delayed\ Start)} = 0.0$ (90% CI -0.04,0.04)
  - **Curves are Not Converging (Parallel)**

ADAGIO Results: Primary Analyses (2 mg/day)





- The 2 mg/day early-start group:
  - showed significant benefits versus placebo in the placebo phase (primary analysis A)
  - did not show superiority versus the delayed-start group at the end of the active phase (primary analysis B)
- The 2 mg/day dose is not approved for marketing. Available doses on the market are 1 mg/day (worldwide) and 0.5 mg/day (in North America only)

ADAGIO – Summary





- ADAGIO is a prospective delayed-start study in PD that uses novel endpoints to determine effects on disease progression
- ADAGIO results support a potential “disease modifying” effect for rasagiline 1 mg/day
- ADAGIO confirms the symptomatic benefit for rasagiline versus placebo in patients with very early disease
- Rasagiline was safe and well tolerated with no specific concerns

Teva Pharmaceutical Industries, Data on File.



Thank You!



Back-up

Innovative Products and Growth Opportunities





Marketed products

- **Multiple Sclerosis Copaxone®**
- **Parkinson's Azilect®**
- **Respiratory QVAR® Albuterol® HFA**

End of Phase III 2008-2010

- **Burns** (Phase III)
- **CIS Copaxone®***
- **Parkinson's** Disease modification**
- **Hemato-oncological** (Phase III)

End of Phase III 2011 and beyond

- **Crohn's disease** (Phase II)
- **Lupus (SLE/LN)** (Phase I)
- **ALS** (Phase II)
- **Oral MS** (Phase III)
- **MS** (Phase II)
- **Hemato-Oncological** (Phase II)
- **Solid Tumor Oncology** (Phase II)

* Study results meet endpoint (announced Dec. 2007); file submitted to authorities in U.S., EU and Canada
** Top-line results announced June 16, 2008; Azilect® 1mg meets all endpoints in phase III trial