Crohn's Disease and MAP Everything Old is New Again

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Financial Disclosure

- **Consulting Product Manager for RedHill Biopharma Ltd. (NASDAQ/TASE:RDHL) an Israeli biotech company developing RHB-104 formulation for Crohn's disease.**
- **CEO and acting Chairman of Giaconda Ltd., AU developer of an earlier formulation of RHB-104 and royalty beneficiary.**

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Where There is Inflammation, Look For Infection

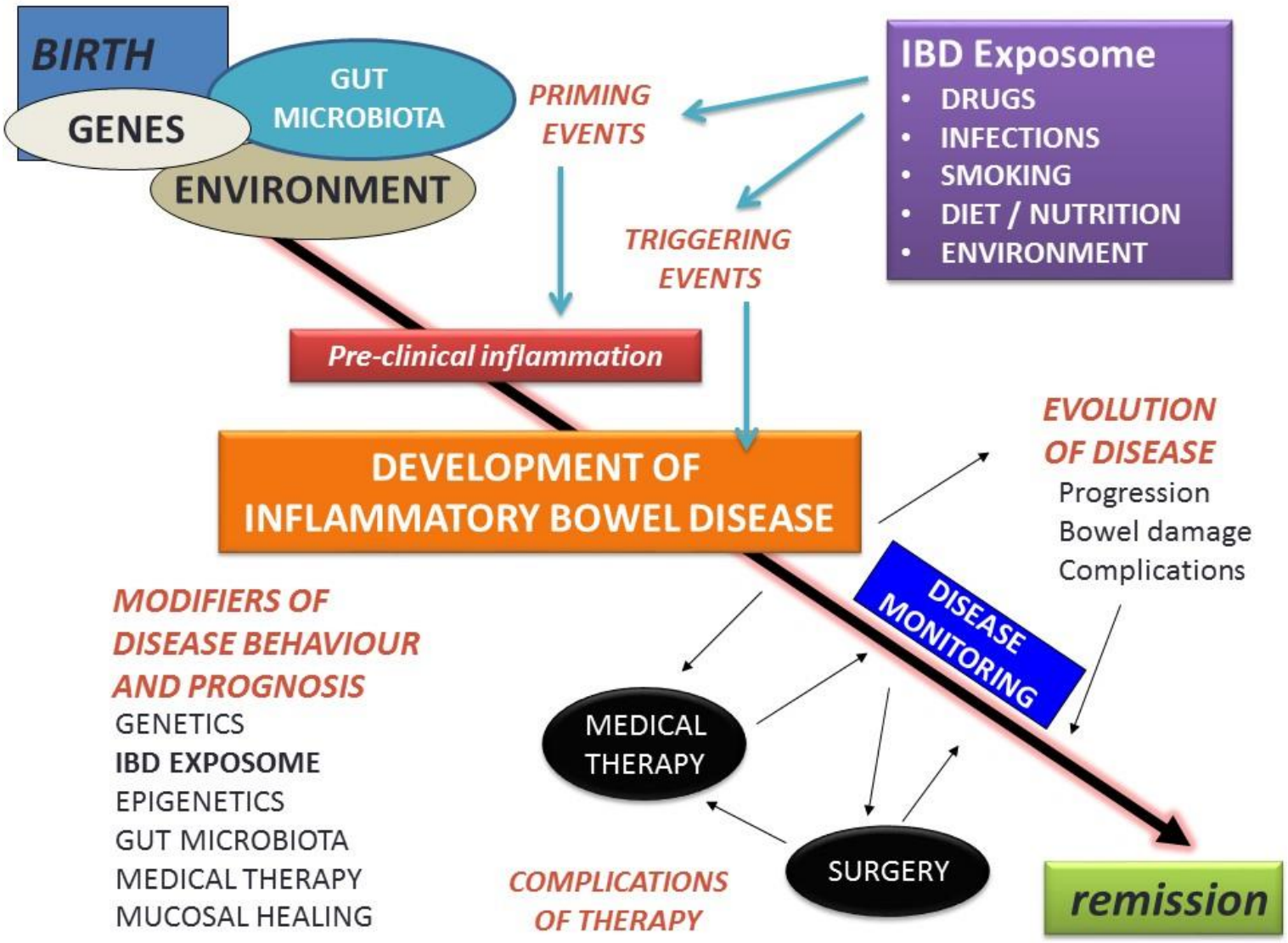
- **Crohn's disease (CD)**
  - Pathologic response to altered gut microbiota
- **RHB-104**
  - Combination antibiotic targeting *Mycobacterium avium paratuberculosis* – a putative cause of CD
- **Paradigm shift not unlike *H. pylori* and peptic ulcer disease**

Crohn's Disease

- **Devastating illness**
- **No cure**
- **Cause unknown**
- **> 1.2 million patients: N America and Europe †**
- **Well characterized**
  - Severe abdominal pain, diarrhea, bleeding, bowel obstruction, and a variety of systemic symptoms
  - Granuloma formation

† Global data report

Pathophysiology of IBD



Current CD Therapy

- **Not curative**
- **Focus on modulation of inflammation**
  - Simply turn down the volume

Early Antibiotic Trials

- **Longstanding belief CD is Johnes-like†.**
- **15 Anti-TB trials in 1980's††.**
- **Some used single and others up to 4 drugs.**
- ***M. tuberculosis* and MAP: different antibiotic sensitivities.**
- **No effective Anti-Tuberculosis combination works in MAP.**
- **Specific Anti-MAP drugs emerged for HIV MAC epidemic.**

† Dalziel T. BMJ 1913; II:1068

†† Greenstein RJ. Lancet. Infect Dis 2003; 3:507-14

Early Anti-MAP Studies

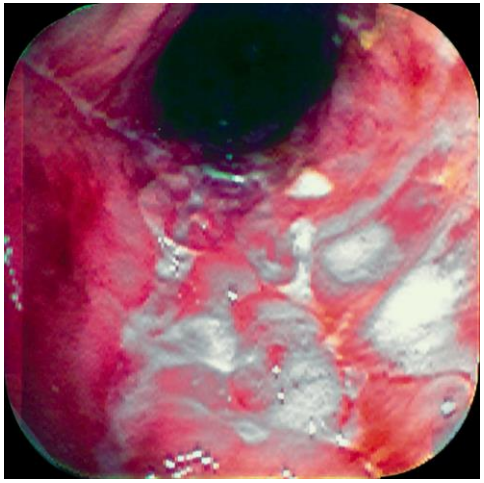
- **Gui *et al*., 1997 – 68% remission**
  - Rifabutin / Clarithromycin or Azithromycin
- **Douglass *et al*., 2000 – 20/28 responded**
  - Rifabutin / Clarithromycin / Clofazimine
- **Shafran *et al*., 2002 – 21/29 responded**
  - Rifabutin / Clarithromycin
- **Borody *et al*., 2002 – 8/12 responded**
  - Rifabutin / Clarithromycin / Clofazimine

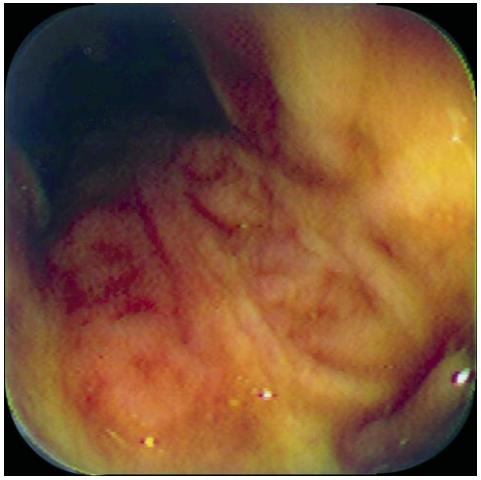
Rationale for Triple Antibiotic Therapy for MAP

- **Mycobacterial infections in humans are complex**
  - Mycobacteria survive and persist within host macrophages as parasites
- **Effective anti-mycobacterial agents require intracellular penetration**
- **ATS/IDSA and WHO advise triple antibiotic therapy for non-tuberculosis mycobacterial disease**

Anti-MAP Therapy in Crohn's patients – Phase II Results †

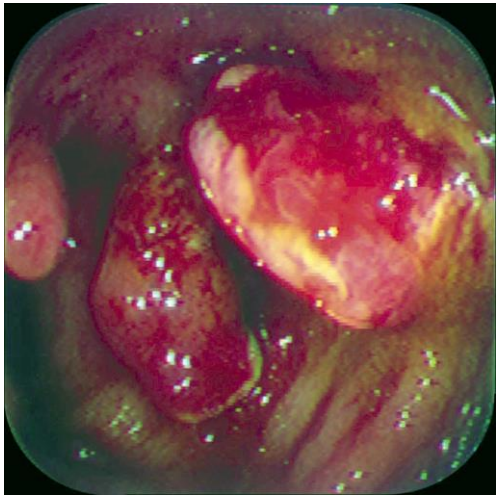
Deep colonic ulcers before anti-MAP therapy

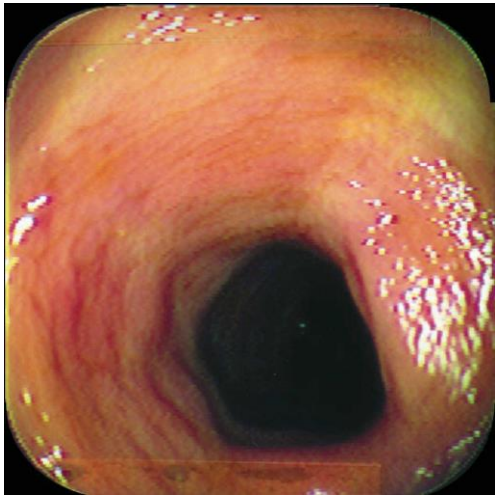




Healing, with scarring, after 20 months on anti-MAP therapy

Extensive pseudo-polyps before anti-MAP therapy



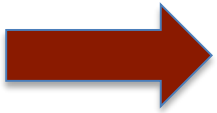


Recovered mucosa after 20 months on anti-MAP therapy

† Borody et al (2002) Digest Liver Dis 34:29-38

Anti-MAP Case Study †

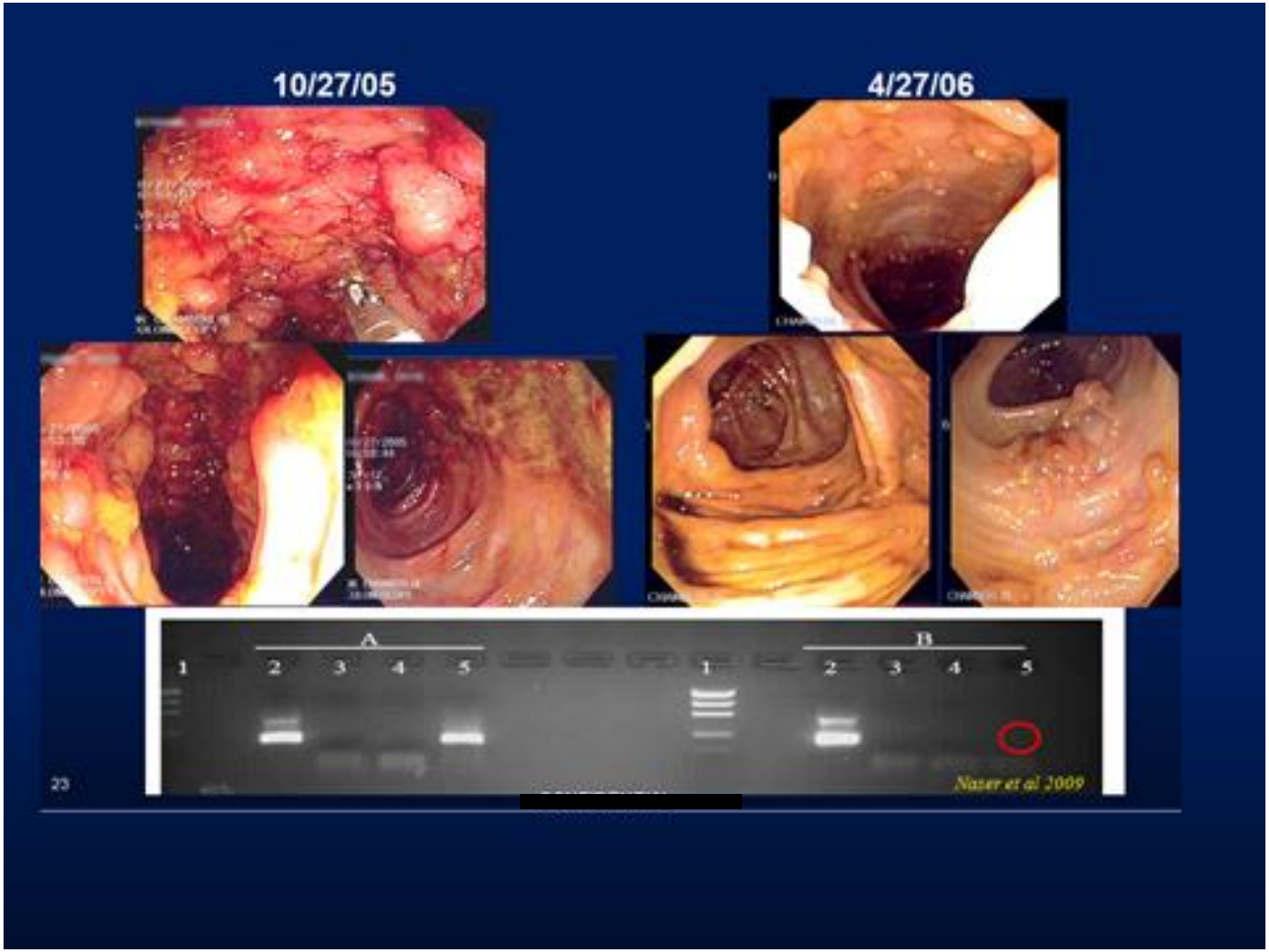
- **63 year old male with severe CD**
  - Colonoscopy - edema, exudates, cobble stoning and ulcers
  - Refused infliximab
  - Treated with Anti-MAP therapy



Mucosal healing and eradication of MAP

† Chamberlin W, Ghobrial G, Chetane, Naser S. Successful treatment of a Crohn's disease patient infected with bacteremic Mycobacterium paratuberculosis.
Am. J. Gastroenterol. 04/2007; 102(3):689-691

Anti-MAP Case Study †



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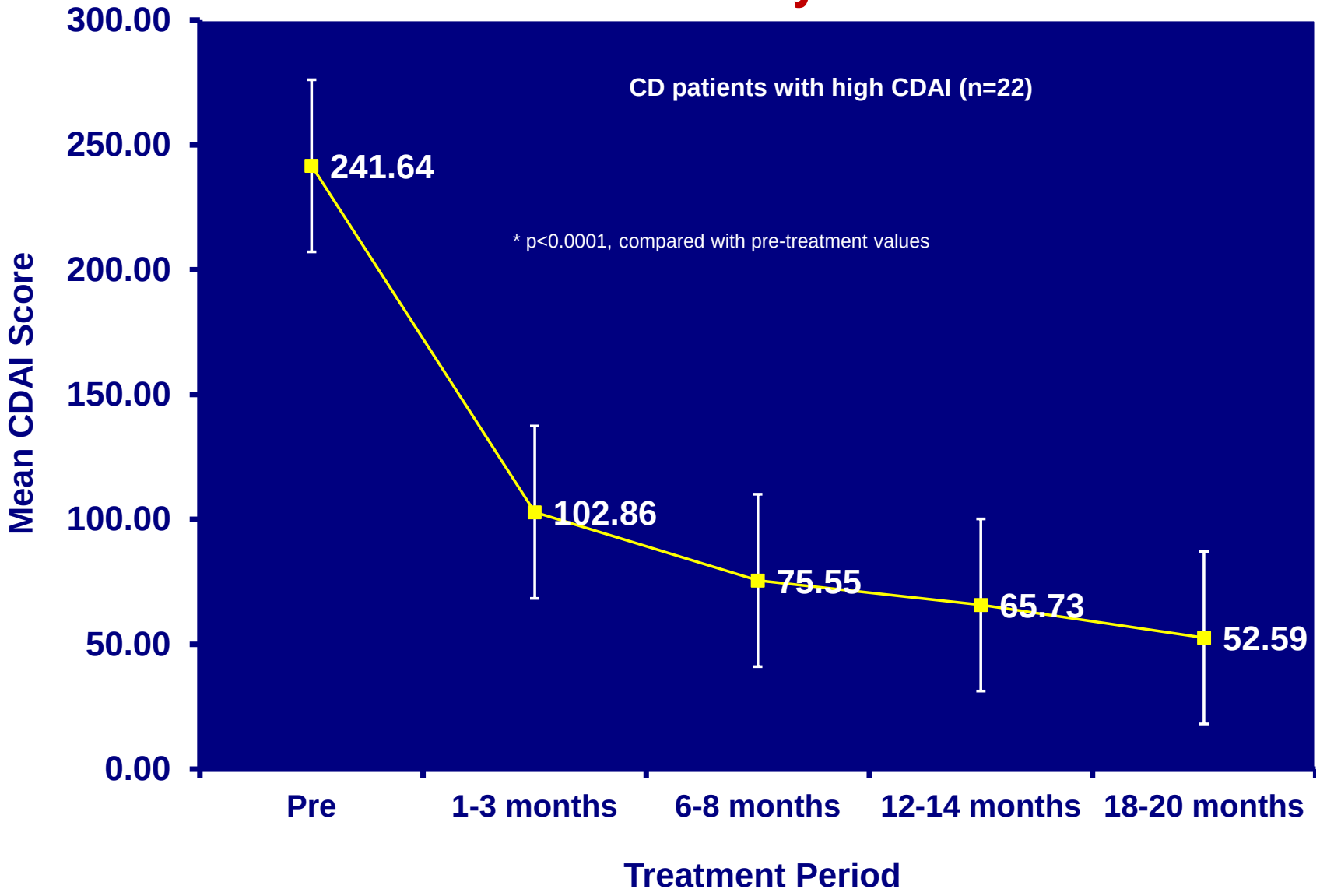
Borody *et al.* 2007- Open Label Phase II Subset Analysis †



† Borody TJ, Bilkey S, Wettstein AR, Lesi S, Pang G, Tye S. Anti-mycobacterial therapy in Crohn's disease heals mucosa with longitudinal scars. *Digestive and Liver Disease* 2007; 39: 438-444.

David has been on AMAT and in remission since 1996

The Australian Financial Review
www.afr.com • Thursday 27 September 2007

Men's Health

Eleven years ago, David Furnari became the first Australian to try the treatment. He is now symptom free. Photo: NIC WALKER

Treatment for Crohn's disease put on the MAP

Jill Margo

For many years, David Furnari's life was ruled by his diseased bowel. The cramping, the bleeding and the running to the toilet up to 15 times a day made an ordinary life impossible.

Furnari was diagnosed with Crohn's disease at the age of 17 and it curtailed his activities so severely that there were times he wanted to end his life.

"I was desperate," he says. "Sometimes the cramps would make me fall to the ground and cry in pain. Countless times I had embarrassing accidents and I couldn't even go on a family picnic unless I could see a toilet."

About 11 years ago, Furnari became the first Australian to try an unorthodox treatment for the condition and today, at 45, he is symptom free and says he doesn't give his bowel a second thought.

He does, however, take a daily low maintenance dose of drugs to keep the disease at bay.

The unorthodox treatment took six weeks to relieve his symptoms and the images on this page show what his bowel looked like before and 20 months after treatment.

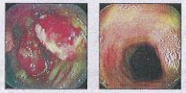
While Furnari is not cured, he has healed substantially and is able to run his motor repair shop in western Sydney and have a full life with his wife and four children.

Crohn's disease can cause inflammation in any area of the digestive tract, from the mouth to the anus. It is thought to be an auto-immune disease and its cause is unknown.

In the large and small bowels, the inflammation can extend deep into the lining and can be complicated by ulceration, narrowing, and the formation of little abnormal passageways between parts of the bowel and other parts of the body.

The standard treatment usually involves a cocktail that includes anti-inflammatory drugs and immunosuppressant agents.

Furnari used to be on this standard treatment. He took it for the first 12 years and says it had only a marginal effect on his symptoms. But it did have long-term adverse effects, particularly on his joints. He has already had one joint replaced and is about to have another. He says his new treatment has only one side effect. It makes him look permanently tanned. "If I spend an hour in the sun, people think I've been in the Caribbean for a month," he says.



Before and 20 months after the treatment.

The new treatment was provided by Thomas Borody, adjunct professor of the Faculty of Science at Sydney's University of Technology, and director of the Centre for Digestive Diseases.

Borody has been fighting a long battle to change the medical paradigm of Crohn's disease. Rather than viewing it as an auto-immune disease, he says it is probably induced by a bug in genetically susceptible individuals.

His leading bug candidate is Mycobacterium avium ss paratuberculosis, known as MAP. This is the bug he successfully treated in Furnari's case and in many others.

Borody's work builds on that of two Perth-based researchers who won the Nobel Prize in 2005. These researchers shifted the paradigm and showed that stomach ulcers are caused by the bug Helicobacter pylori.

Before their discovery, no one believed a bug could survive in the acidic environment of the stomach.

As many people now know, this stomach bug can be eradicated by a cocktail of antibiotics. After the discovery, it was Borody who developed and patented the first effective triple therapy to eradicate Helicobacter pylori.

This made him think that if a bug could cause ulcers in the stomach, perhaps a bug was causing ulceration further down the digestive system in the small and large bowels.

He has been working on MAP and Crohn's for the past 13 years and continues to encounter scepticism from the medical profession.

But he has shown that a combination of three drugs, which he calls Myoconda, can overcome it.

While Myoconda can't eradicate MAP, it can force it into silence where it causes no symptoms and allows the bowel to heal.

Around the world, about a dozen specialists are now working with MAP and the current estimate is that half the people with Crohn's have detectable MAP.

The remainder may have it too, but detection is problematic because MAP typically sheds its cell wall when it enters humans and becomes an intracellular infection.

The science to detect MAP is only beginning to emerge and Borody is working with Saleh Naser, a professor at the University of Central Florida to validate the methods.

If a patient has MAP, it can take between six and 16 weeks of treatment before their bowel heals.

Borody has 800 patients with Crohn's in his practice and because of the cost, says only 20 per cent are treated for MAP.

The drugs have to be imported and full therapy costs about $350 a month. At present, patients are usually treated with a full dose for two years. If they have had no inflammation or scarring for two years, they go onto a low maintenance dose.

"If we were offering a cure, like they do for Helicobacter, then we would have a long line of patients outside the surgery," Borody says.

In June, he published a study in the journal *Digestive and Liver Disease* showing how anti-MAP therapy results in profound healing not experienced with standard anti-inflammatory and immunosuppressant drugs. The journal's editor said that this healing should become the new gold standard for treating Crohn's.

The anti-MAP therapy resulted in novel scars that appeared to recede over time as the inflammation and ulceration resolved.

Borody says independent confirmation of the effectiveness of anti-MAP therapy is now needed.

In 2005, the biotech company Giaconda was listed on the Australian Stock Exchange to make this therapy available to people suffering from Crohn's.

Earlier this year, the US Food and Drug Administration approved an IND (investigational new drug application) for Myoconda.

Rationale for RHB-104 Triple Antibiotic Treatment of CD

- **Rifabutin, clarithromycin, and clofazimine active against *Mycobacterium avium complex* (MAC)**
  - *M. avium paratuberculosis* (MAP) is a subspecies of MAC
  - All active intracellularly
- **Current CD therapies have some anti-MAP activity**
- **Previous clinical experience**
  - All clinical efficacy studies in CD have included “all comers”
  - RHB-104 is intended for all CD patients

MAP US First Phase III Study Dose Escalation - Ongoing

Individual Capsule Components of RHB-104:

Clarithromycin	**95mg**
Rifabutin	**45mg**
Clofazimine	**10mg**

Weekly Dose Escalation	Week 1	Week 2	Week 3	Week 4	Week 5+	Target dose in Active Arm
Active & Placebo Arms	**1 capsule bid**	**2 capsules bid**	**3 capsules bid**	**4 capsules bid**	**5 capsules bid**	Clarithromycin - 950 mg Rifabutin - 450 mg Clofazamine - 100 mg

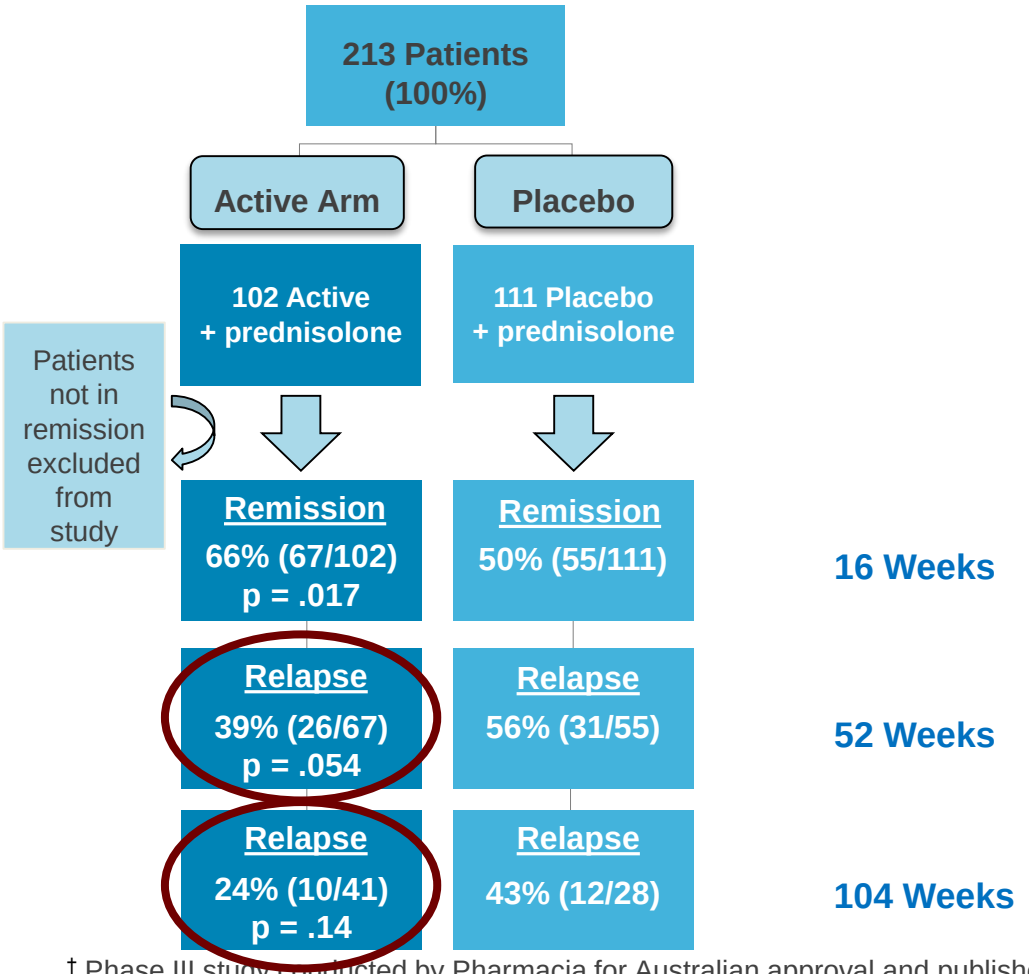
Pfizer Phase III Primary Objective †

To determine whether the % of patients who experience at least one relapse of Crohn's Disease between weeks 16-52 given proven remission at week 16, was significantly different between those treated with anti-paratuberculosis therapy (APT) or placebo.

† Selby W, Pavli P, Crotty B, Florin T, Radford-Smith G, Gibson P, Mitchell B, Connell W, Read R, Merrett M, Hooiee, Hetzel D, et al, Two-Year Combination Antibiotic Therapy With Clarithromycin, Rifabutin, and Clofazimine for Crohn's Disease, *Gastroenterology* 2007, 132:2313-2319.

Pfizer Study Showed Strong Signs of Efficacy †

Original Study Relapse Endpoint
Skewed denominator at week 16

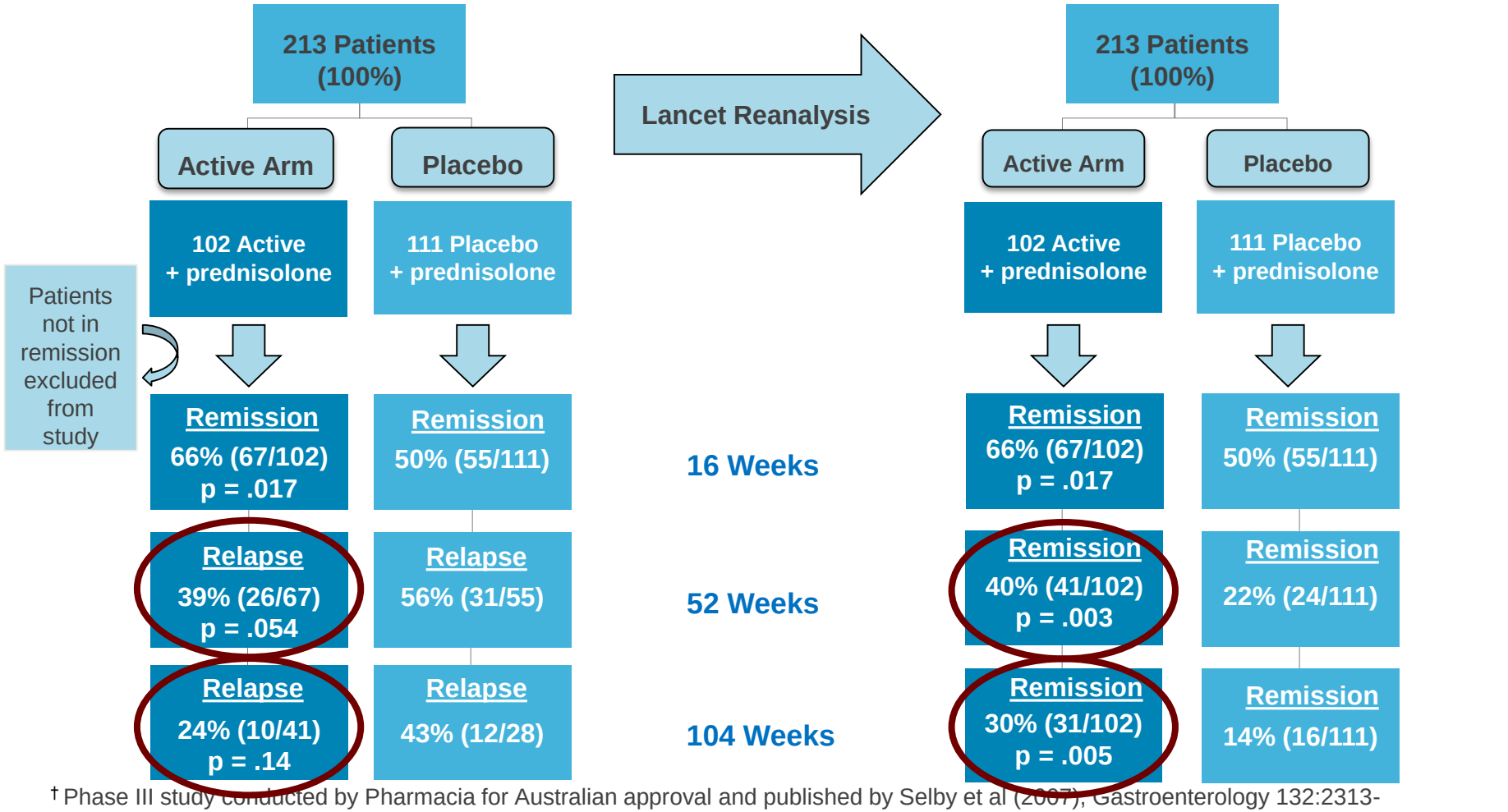


† Phase III study conducted by Pharmacia for Australian approval and published by Selby et al (2007), Gastroenterology 132:2313-2319.; Reanalysis published by Behr and Hanley (2008), Lancet Infectious Diseases 8:344. including all subjects randomized at the beginning of the study, disregarding any occurrence following randomization

Pfizer Study Showed Strong Signs of Efficacy

Original Study Relapse Endpoint †
Skewed denominator at week 16

Remission Endpoint Reanalysis ††
Randomized denominator at time 0



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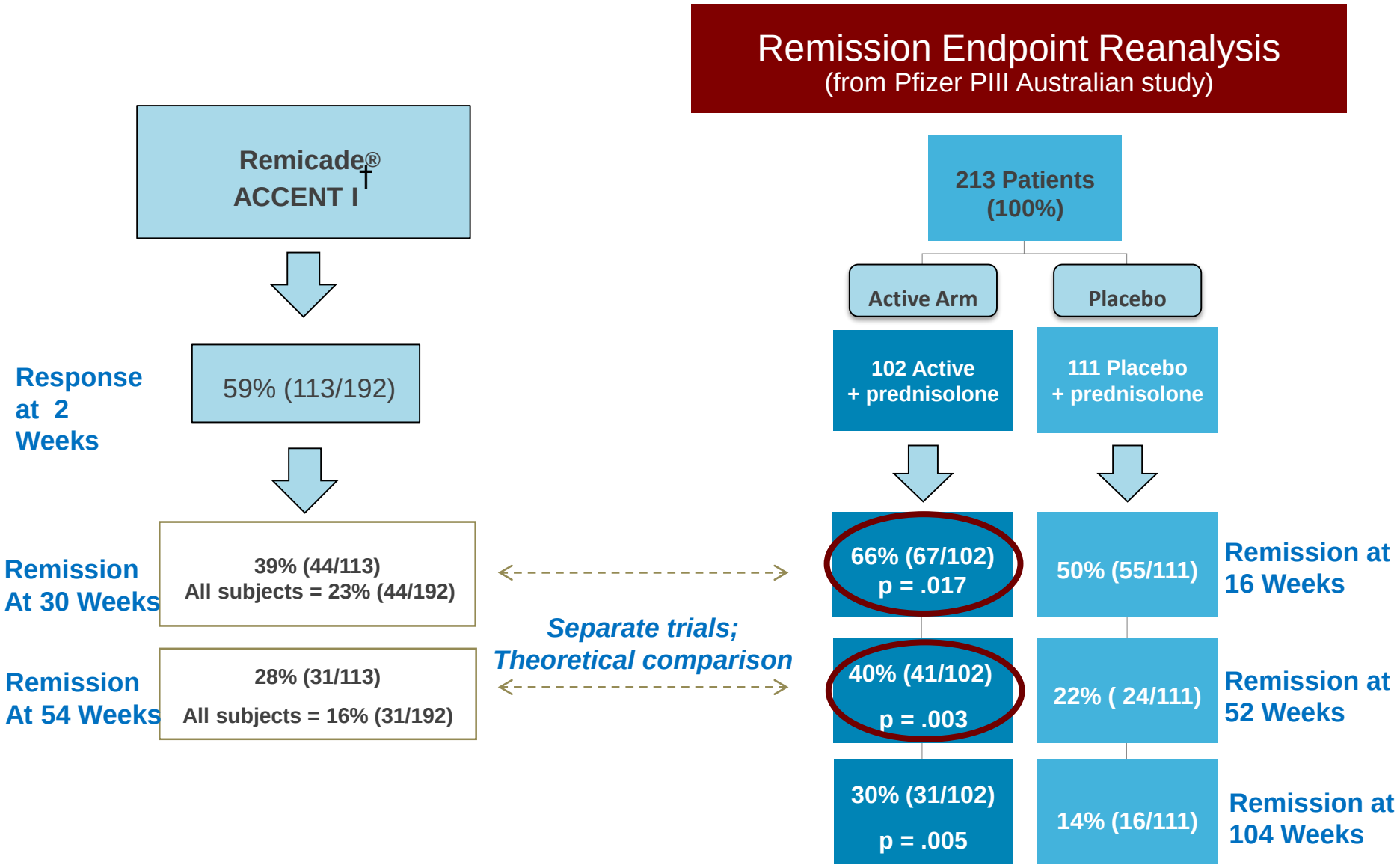
Pfizer Study Data Could Have Compared Favorably to Remicade®



† Hanauer et al, (2002), The Lancet 359: 1541-1549. study similar to the reanalysis conducted by Behr and Hanley

RHB-104 MAP US First Phase III Study - Ongoing

- Multi-center, randomized, double-blind, placebo-controlled, parallel group study
- 270 moderate to severe CD subjects randomized 1:1
- CDAI score of ≥220 and ≤450 at baseline
- Add-on to 5-ASA, immunomodulators, steroids, selective biologics
- Up to 120 sites in US, Canada, Israel, Australia, New Zealand, and selected EU countries
- Primary endpoint
  - Remission at 26 weeks
- Lead investigator – Prof. David Graham MD
- Clinicaltrials.gov search Crohn's disease, Anti-MAP, RHB-104

Additional Study Endpoints

- **Secondary and exploratory endpoints include:**
  - Maintenance of remission through week 52
  - Time and duration of remission/response
  - CRP and fecal calprotectin
- **Efficacy outcome measures in relation to MAP**
- **Health related quality of life using IBDQ and SF 36**
- **Steroid discontinuation**
- **Safety**
- **Population PK**
- **CDEIS**
- **Validation of MAP assay**

Conclusions

- ***H. pylori* was strongly associated with ulcers**
- **Eradicating *H. pylori* is proven to treat ulcers**
  - H. pylori association is causal
- **MAP and CD are strongly associated**
- **If anti-MAP therapy treats CD and eradicates MAP, we will have proven the association is causal**

Questions?

RedHill Biopharma