COSMO Pharmaceuticals

R&D Day

Zuerich

December 1, 2010

Safe harbor

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Cosmo R& D day: the evolution of Cosmo

- **Presenters**
  - Mauro Ajani, CEO
  - Luigi Moro, CSO
  - Chris Tanner, CFO

- **The entrepreneurial challenge**
  - From contract drug manufacturer
  - To MMX based products focused on IBD
  - To larger diseases and new MMX applications

- **The MMX technology**

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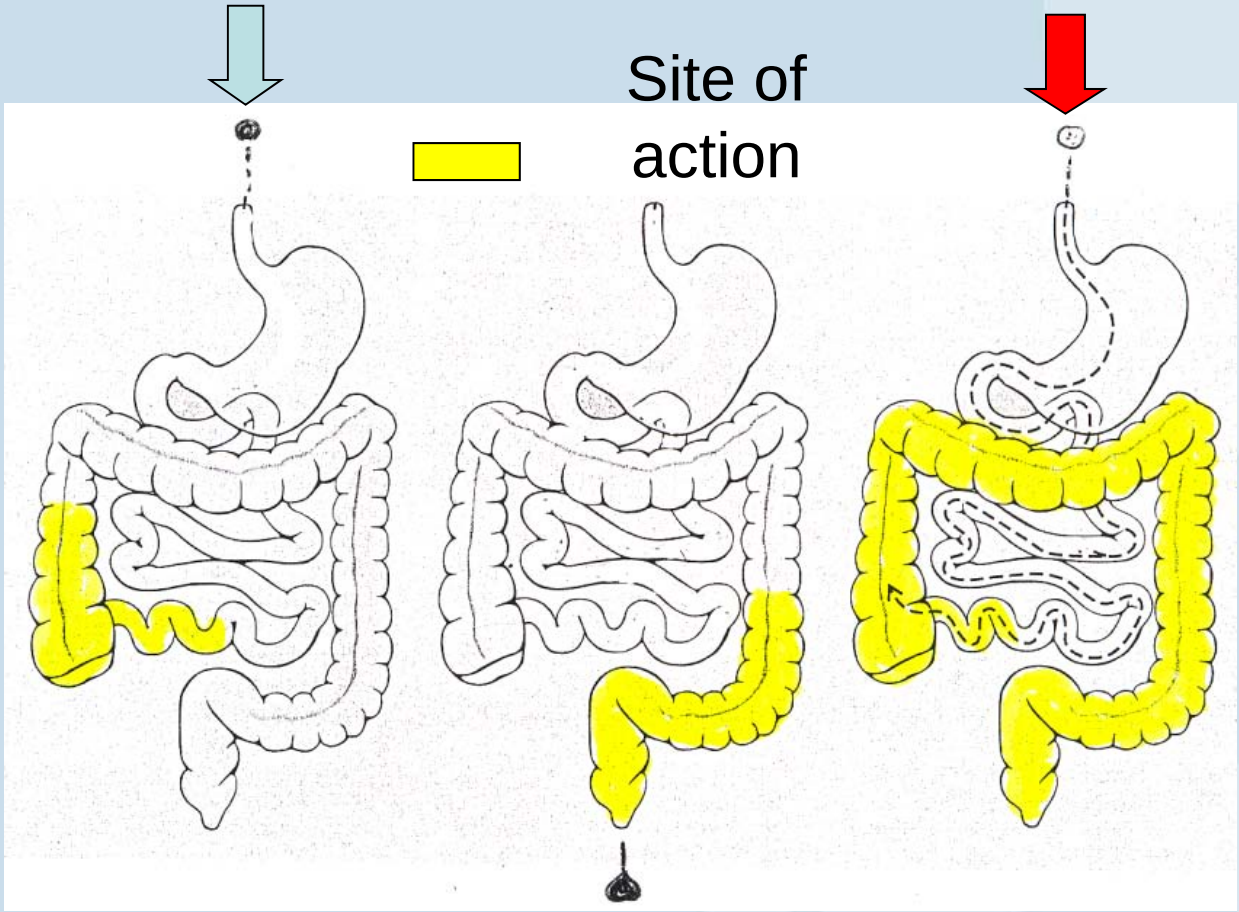
IBD medications: sites of action
MMX™ tablets vs. other dosage forms



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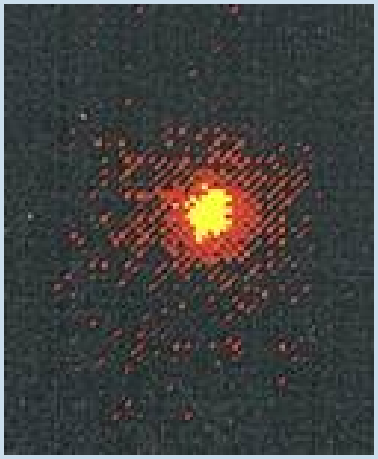
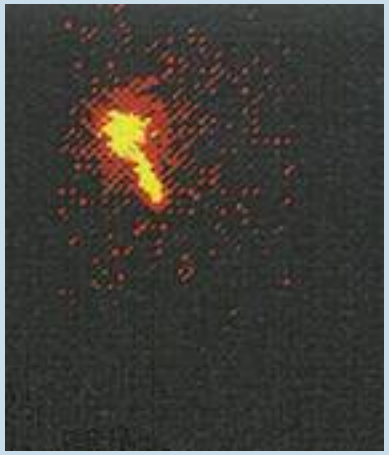
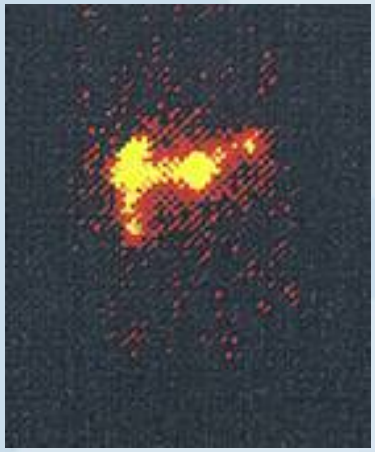
MMX: Proving extended release and persistence of radioactive traces released by MMX in gut



1h 30’ duodenum



4h 30’ ascending colon



7h 30’ trasverse colon

10h trasverse colon

16h descending colon

24h rectum

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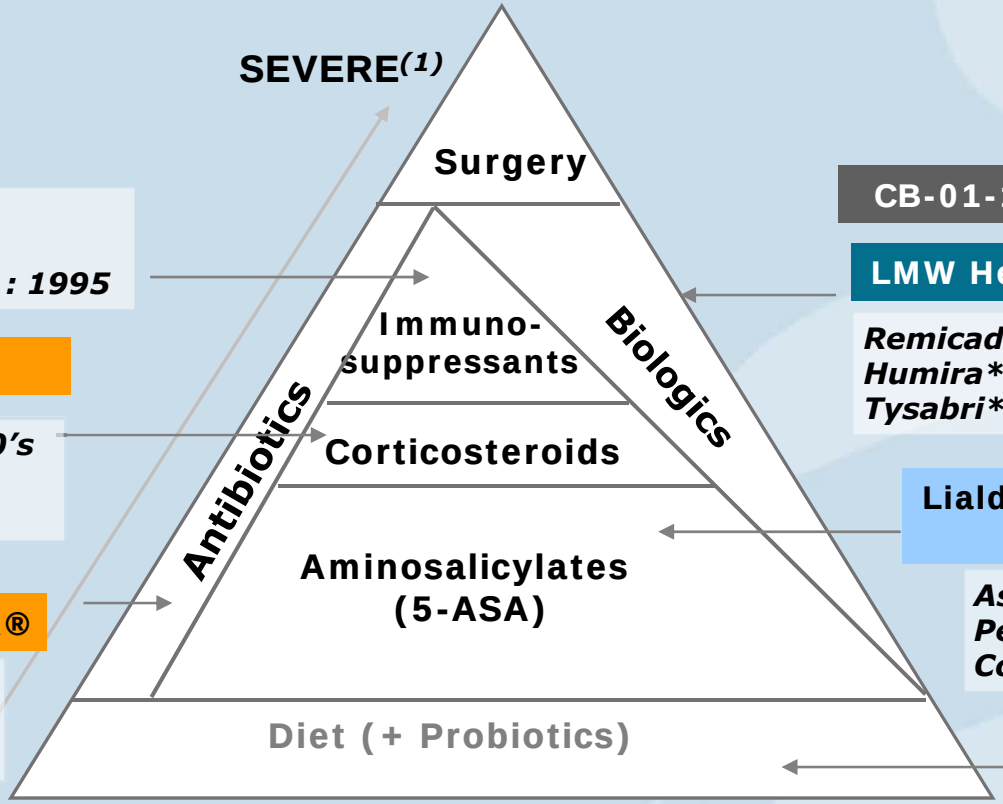
Focus on IBD, a disease with little recent innovation



CB-01-09

Imurek*: 1981
Sandimmun*: 1983
Sandimmun Neoral* : 1995

Budesonide MMX®

Prednisolone: late 50's
Budenofalk° : 1998
Entocort EC *: 2001

Rifamycin SV MMX®

Flagyl*: 1963
Ciproxin*: late 80's
Xifaxan*: 2004

CB-01-12

LMW Heparin MMX®

Remicade*: 1999
Humira*: 2003
Tysabri*: 2008

Lialda® / Mezavant ® / Mesavancol ®
Launch date: 2007

Asacol*: 1992
Pentasa* : 1993
Colazal*: 2000

Zacol NMX®

1. Status of disease severity
° EU
** US*

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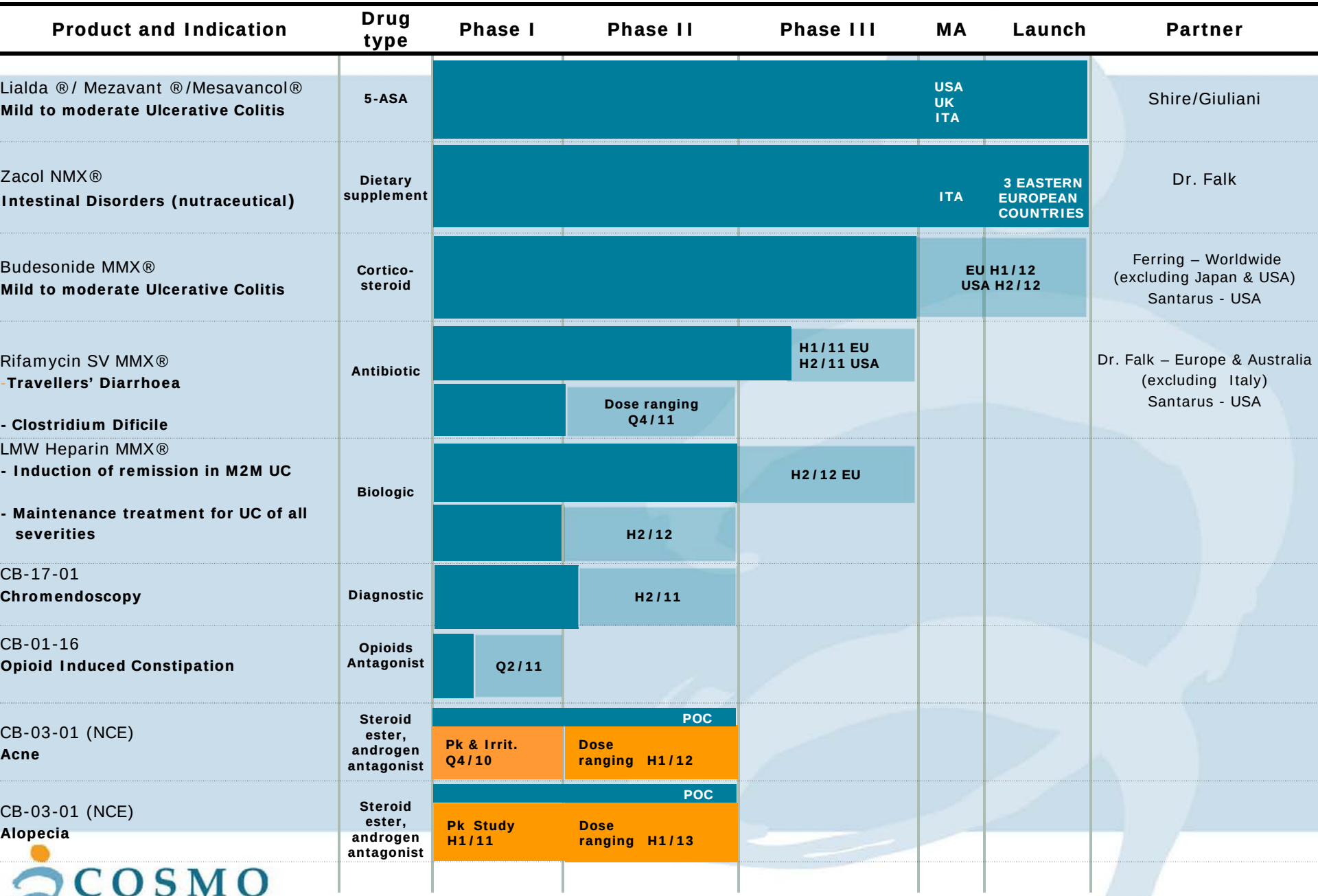
Cosmo's pipeline



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- **Lialda MMX**

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The first product: Lialda®

- The active ingredient Mesalamine [or 5-ASA or amino salicylic acid] is an off-patent chemical entity, used since the years ‘60 in the intestinal inflammatory diseases

- The product is indicated for Patients with Ulcerative Colitis of mild to moderate severity

- Market entry in March 2007. revenue 2009 $ 210 m. Analysts projections for 2010: $ 293 m (Europe will come on-stream); for 2011 $ 382 m

- Competing products in 2009 were Asacol $ 684 m; Pentasa $236 m; Canasa $ 95 m all with increased sales but decreasing TRX.

What does the ANDA filing mean

- Zydus filed aNDA for 1200 mg Mesalamine tablets in May 2010; Shire has filed law suit for patent infringement
  - Whilst this is pending the FDA will not act on the ANDA
- To date FDA required generics need to prove bioequivalence for 5-ASA and pro-drugs in IBD by conducting clinical trials
- New ruling by FDA in July 2010 to determine bioequivalence
  - in vitro dissolution tests and
  - comparative PK/safety studies
- Demonstrating identical dissolution/PK profile to our extended release MMX technology will be very challenging
- Shire is completing clinical trials for Lialda in Diverticulitis. If FDA approves, they will be granted a New Use/New Clinical Studies exclusivity for Lialda for an additional three years

Cosmo revenue scenarios for Lialda

- **Diverticulitis approved, Patent challenge loses**
  - Peak sales $ 1 b, discount rate 10%, post tax NPV per share of CHF 7.28
- **Diverticulitis not approved, Patent challenge loses**
  - Peak sales $ 590 m, discount rate 10%, post tax NPV per share of CHF 6.10
- **Diverticulitis approved, Patent challenge succeeds**
  - Peak sales $ 543 m, loss of sales 50%, discount rate 10%, post tax NPV per share of CHF 5.96
- **Diverticulitis not approved, patent challenge succeeds**
  - Peak sales $ 500 m, loss of sales 50%, post tax NPV per share of CHF 5.18

- **Budesonide MMX**

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NORTH AMERICA & INDIA

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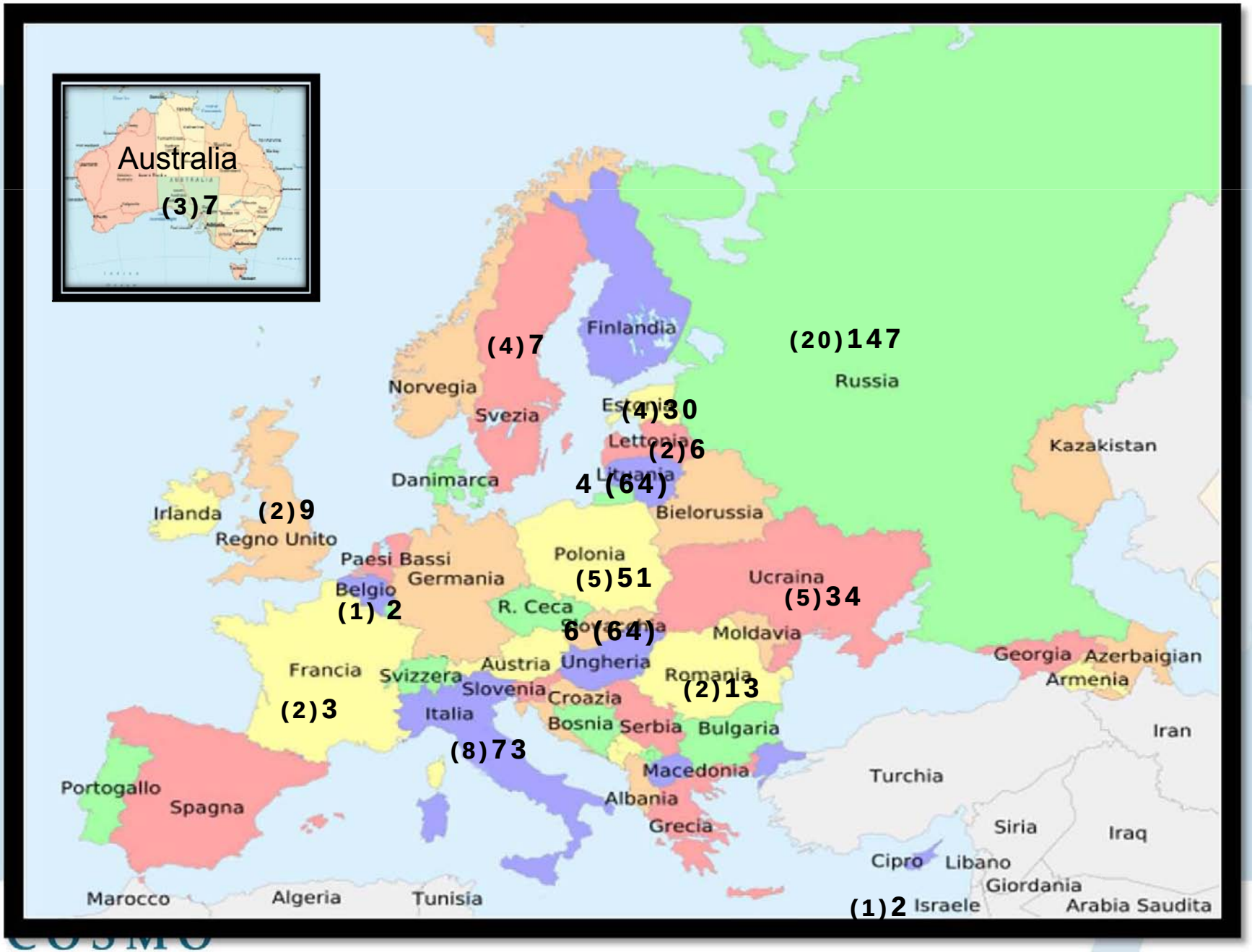
EUROPE



Pharmaceuticals

Preliminary Results of EU Phase III study
Efficacy: primary endpoint attained

Treatment arm	Number of patients ITT	Patients in remission	P-value
Budesonide MMX 9 mg	109	19 (17.4%)	0.0047*
Budesonide MMX 6 mg	109	9 (8.3%)	0.2876
Entocort EC 3 x 3 mg[(a)]	103	13 (12.6%)	0.0481**
Placebo	89	4 (4.5%)	

Treatment arm	Number of patients PP	Patients in remission	P-value
Budesonide MMX 9 mg	84	19 (22.6%)	0.0047*
Budesonide MMX 6 mg	73	8 (11.0%)	0.2922
Entocort EC 3 x 3 mg[(a)]	72	12 (16.7%)	0.0483**
Placebo	67	4 (6.0%)	

*Statistically significant vs placebo at 0.025
** Statistically significant vs placebo at 0.05
[(a)]Not powered to show statistical difference between MMX arms and Entocort

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Preliminary Results of US Phase III study
Efficacy: primary endpoint attained

Treatment arm	Number of patients ITT	Patients in remission	*P-value*
Budesonide MMX 9 mg	123	22 (17.9%)	*0.0143**
Budesonide MMX 6 mg	121	16 (13.2%)	*0.1393*
Asacol reference arm[(a)]	124	15 (12.1%)	*0.2200*
Placebo	121	9 (7.4%)	

Treatment arm	Number of patients PP	Patients in remission	*P-value*
Budesonide MMX 9 mg	69	20 (29.0%)	*0.0027**
Budesonide MMX 6 mg	72	11 (15.3%)	*0.2110*
Asacol refernece arm[(a)]	73	10 (13.7%)	*0.3144*
Placebo	61	5 (8.2%)	

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Preliminary Results of Phase III studies ITT populations analysis

All patients included in the ITT populations of single trials are considered

EU - Treatment arm	Number of patients	Patients in remission	*P-value*
Budesonide MMX 9 mg	109	19 (17.4%)	*0.0047**
Budesonide MMX 6 mg	109	9 (8.3%)	*0.2876*
Entocort EC 3 x 3 mg[(a)]	103	13 (12.6%)	*0.0481***
Placebo	89	4 (4.5%)	

US - Treatment arm	Number of patients	Patients in remission	*P-value*
Budesonide MMX 9 mg	123	22 (17.9%)	*0.0143**
Budesonide MMX 6 mg	121	16 (13.4%)	*0.1393*
Asacol 2x400mg TID	124	15 (12.1%)	*0.2200*
Placebo	121	9 (7.4%)	

EU + US - Treatment arm	Number of patients	Patients in remission	*P-value*
Budesonide MMX 9 mg	232	41 (17.7%)	*0.0002**
Budesonide MMX 6 mg	230	25 (10.9%)	*0.0809*
Placebo	210	13 (6.2%)	

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Preliminary Results of Phase III studies
PP populations analysis

All patients included in the PP populations of single trials are considered

EU - Treatment arm	Number of patients	Patients in remission	*P-value*
Budesonide MMX 9 mg	84	19 (22.6%)	*0.0047**
Budesonide MMX 6 mg	73	8 (11.0%)	*0.2922*
Entocort EC 3 x 3 mg[(a)]	72	12 (16.7%)	*0.0481***
Placebo	67	4 (6.0%)	

US - Treatment arm	Number of patients	Patients in remission	*P-value*
Budesonide MMX 9 mg	69	20 (29.0%)	*0.0027**
Budesonide MMX 6 mg	72	11 (15.3%)	*0.2110*
Asacol 2x400mg TID	73	10 (13.7%)	*0.3144***
Placebo	61	5 (8.2%)	

EU + US - Treatment arm	Number of patients	Patients in remission	*P-value*
Budesonide MMX 9 mg	153	39 (25.5%)	*<0.0001**
Budesonide MMX 6 mg	145	19 (13.1%)	*0.0989*
Placebo	128	9 (7.0%)	

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Preliminary Results of US Phase III study
Safety – Treatment Emergent Adverse Events (TEAEs)

Treatment group	Safety Population	TEAEs				
		TOTAL	MILD	MOD.	SEVERE	TREATMENT RELATED
9 mg	127	73	30	35	8	**36**
6 mg	126	74	33	29	12	**35**
Asacol	127	80	39	35	6	**31**
Placebo	129	80	31	34	15	**34**

Preliminary Results of EU Phase III study
Safety – Treatment Emergent Adverse Events (TEAEs)

Treatment group	Safety Population	TEAEs				
		TOTAL	MILD	MOD.	SEVERE	TREATMENT RELATED
9 mg	128	71	27	32	12	**33**
6 mg	128	80	36	38	5	**28**
Entocort	126	69	30	29	10	**29**
Placebo	129	57	18	32	5	**31**

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Preliminary Results of US Phase III study
Safety - Plasma cortisol

Treatment arm	screening	Visit 2	Visit 3	Visit 4	Final visit
BUD MMX 9 mg	361.0	333.4	204.6	176.9	253.7
BUD MMX 6 mg	315.0	363.0	242.2	252.4	283.7
Asacol 6x400 mg	349.2	357.1	333.1	313.1	331.9
Placebo	332.2	333.8	330.7	336.5	331.9

NB: Central laboratories quote a normal range of **138-690** nmol/L for morning cortisol

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Preliminary conclusions of EU + US Phase III study

- **Significant superiority vs. placebo** in the primary endpoint (-> allows product submission of MAA)
- **Similar primary end point remission rate** in EU and US studies
- **Higher remission rates for 9 mg than 6 mg**
- **Higher remission rates than Entocort and Asacol**
- **Tolerability** profile and **side effects** comparable to **placebo**

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INFLAMMATORY BOWEL DISEASE: A PRACTICAL APPROACH, SERIES #26

Seymour Katz, M.D., Series Editor

Remission in Trials of Ulcerative Colitis: What Does It Mean?

by Simon Travis and Lotte Dinesen

Measurement of disease activity in ulcerative colitis is critical in determining whether new therapies are effective, but there is no gold standard for measuring disease activity in ulcerative colitis. Not only is no single disease activity index widely accepted, but there is also no generally accepted definition of remission. Remission rates vary by as much as two-fold depending on the definition of remission. When two trials of 4.8 g mesalamine were evaluated according to the remission endpoint used for two trials of infliximab for active ulcerative colitis, apparent remission increased from 20.0% to 44.9%. Physicians and healthcare professionals should pay attention to the definition of remission being used as a measure of clinical efficacy in clinical trials. Interobserver variation in endoscopy scoring alone can influence the absolute remission rate by 10%–16%. Registration remission, which depends primarily on endoscopy and absence of rectal bleeding, is most subject to this influence. Clinical remission (absence of rectal bleeding and normal stool frequency) is used in clinical practice. Steroid-free remission is what matters to patients. The definition of remission needs to be validated if the results of clinical trials are to be compared.

What is remission? Substantial variations in medians

Placebo Rates of Remission and Response Based on Various Definitions of Outcomes

Outcome	No. of studies	% Pooled estimate (95% CI)	*P* for heterogeneity	Range, %	Median, %
Remission					
All definitions	27	13 (9–18)	<.001	0–40	12
UCDAI = 0	6	5 (2–16)	.025	0–21	5
UCDAI < 3	6	17 (10–28)	.08	4–33	21
PGA = 1	2	13 (9–19)	.70	12–14	13
Rachmilewitz Index ≤ 4	2[a]	39 (29–50)	.67	35–40	38
Endoscopic	14	18 (13–24)	.001	0–37	19
Histologic	8	8 (3–19)	<.001	0–44	6
Response					
All definitions	34	28 (23–33)	<.001	0–67	30
↓ UCDAI ≥ 3	5	30 (15–50)	.004	9–56	36
↓ UCDAI ≥ 2	3	52 (40–65)	.45	47–67	48
PGA ≤ 2	2	32 (25–39)	.26	27–36	32

PGA, Physician's Global Assessment.

[a]One study also included a decrease of the index by ≥ 2 points for defining remission.

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What is remission? Substantial differences in placebo remission rates

Placebo Remission Rates of the 12 Studies Defining Remission as a UCDAI of 0 or a UCDAI of Less Than 3

Study	Placebo sample size	Study duration, wk	Entry UCDAI score	Definition of remission, UCDAI score	Placebo remission rate, %
Nikolaus et al[34]	7	N/A[a]	8.5	0	0
Sandborn et al[27]	33	4	7.9	0	0
Vernia et al[38]	27	6	6.1	<3	3.7
Schroeder et al[3]	38	6	7.7	0	5
Sandborn et al[21]	20	4	8	0	5
Williams et al[9]	13	6	7.4	0	7.7
Sandborn et al[36]	28	4	7.5	<3	11
Steinhart et al[23]	19	6	7.4	<3	16
Roberts et al[26]	44	8	6.8	0	20.5
Scheppach[22]	16	8	7.6	<3	25
Probert[35]	20	6	8.5	<3	30
Vernia[31]	15	6	6.1	<3	33.3

N/A, not applicable.
[a]Variable.

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What is remission?

- **Definition of Registration remission as determined by the Regulator, has been getting increasingly stringent**
  - Definition of patients has become more precise
    - Use of colonoscopy at entry
    - Use of histology at entry
  - Definitions of clinical endpoints has become more stringent
    - Move from UCDAI 2 to ≤1 or 0
  - Measurement of clinical endpoints has become more precise
    - From patient observation, to sigmoidoscopy, to colonoscopy, to two colonoscopies

Budesonide MMX®: going forward

- **Projected filing**
  - MAA in EU in H1 2011; NDA for USA H2 2011
- **Market entry**
  - A year later
- **Market**
  - In USA there is no steroid approved for mild to moderate UC
  - 2009 Entocort sales at $ 237 m equal to Lialda® for a patient base 2/3 that of Lialda®
- **Projected peak sales**
  - USA $150-250 million
    - targeted at the ~60-80% of patients that do not get remission with 5 ASA's
    - After assessing safety data the entire 5 ASA market could be targeted
  - RoW EUR 100 million
- **Licensing revenue**
  - USA: licensed to Santarus; 12-14% royalties; plus ~10% COGS for US
  - RoW: 25-33% total return
  - Japan: unpartnered

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Cosmo Revenue scenarios for Budesonide MMX®

- **Business case**
  - Between 60% (Lialda study) and 86% (Cosmo/Santarus study) of mild to moderate patients do not go into remission with 5 ASAs
    - In the US ~850'000 persons have UC; ~60% are mild to moderate
    - In the EU ~850'000 persons have UC, ~60% are mild to moderate
  - Assuming 2 flares per year, between 1.2 m and 1.4 m flares p.a. are ineffectively treated with 5 ASAs in USA and EU
    - This is a market potential of $1-1.4 b
  - 5 ASAs market in US is $ 1.4 b p.a.
  - Cost per flare is around $ 840
  - Patents expire 2022
  - Economics of licensing agreement in US and EU are such that pre tax NPV at 10% discount rate amounts to ~84% of peak sales.
    - 50% market penetration, Peak sales of $ 500 m, post tax NPV pS of CHF 19.38
    - 40% market penetration, Peak sales of $ 400 m, post tax NPV pS of CHF 15.50
    - 30% market penetration, Peak sales of $ 300 m, post tax NPV pS of CHF 11.63
    - 15% market penetration, Peak sales of $ 150 m, post tax NPV pS of CHF 5.81

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- **Rifamycin SV MMX**

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Rifamycin SV MMX®

- **The chemical entity**
  - Broad-spectrum antibiotic belonging to the ansamycin family
  - New chemical entity in the US, Off-patent in EU
- **Market need**
  - Need for a non-absorbable antibiotic that does not sterilize bacteria in upper gut
  - Does not promote bacterial resistance
- **Competing products**
  - Rifaximin € 200 m
  - Ciprofloxacin € 331 m
- **Partnerings**
  - In USA and EU
  - Not partnered in Latin America, Asia nor Africa

Rifamycin SV MMX®: Status and opportunities

Clinical development

Patient recruiting for phase III trials in the US and EU ongoing

- Primary clinical endpoint: time to last unformed stool (TLUS)
- EU trial: single phase III trial on around 700 patients, 400 mg b.i.d. X 72 hours, non inferiority vs. Ciprofloxacin 500 mg b.i.d
- US trials: two consecutive phase III studies on 300 patients each, 400 mg b.i.d. X 72 hours, superiority vs. placebo

Opportunities

- Highly effective against Clostridium Dificile Associated Disease (CDAD)
- Probably effective in Hepatic Encephalopathy
- Due to its anti-inflammatory properties, Rifamycin SV MMX®
  - Could also be used for IBD supportive therapies
  - Could be the drug of choice for the treatment of Diverticulitis, a chronic disease that affects more than 60% of people over the age of 60

CB-01-05
LMW Heparin MMX

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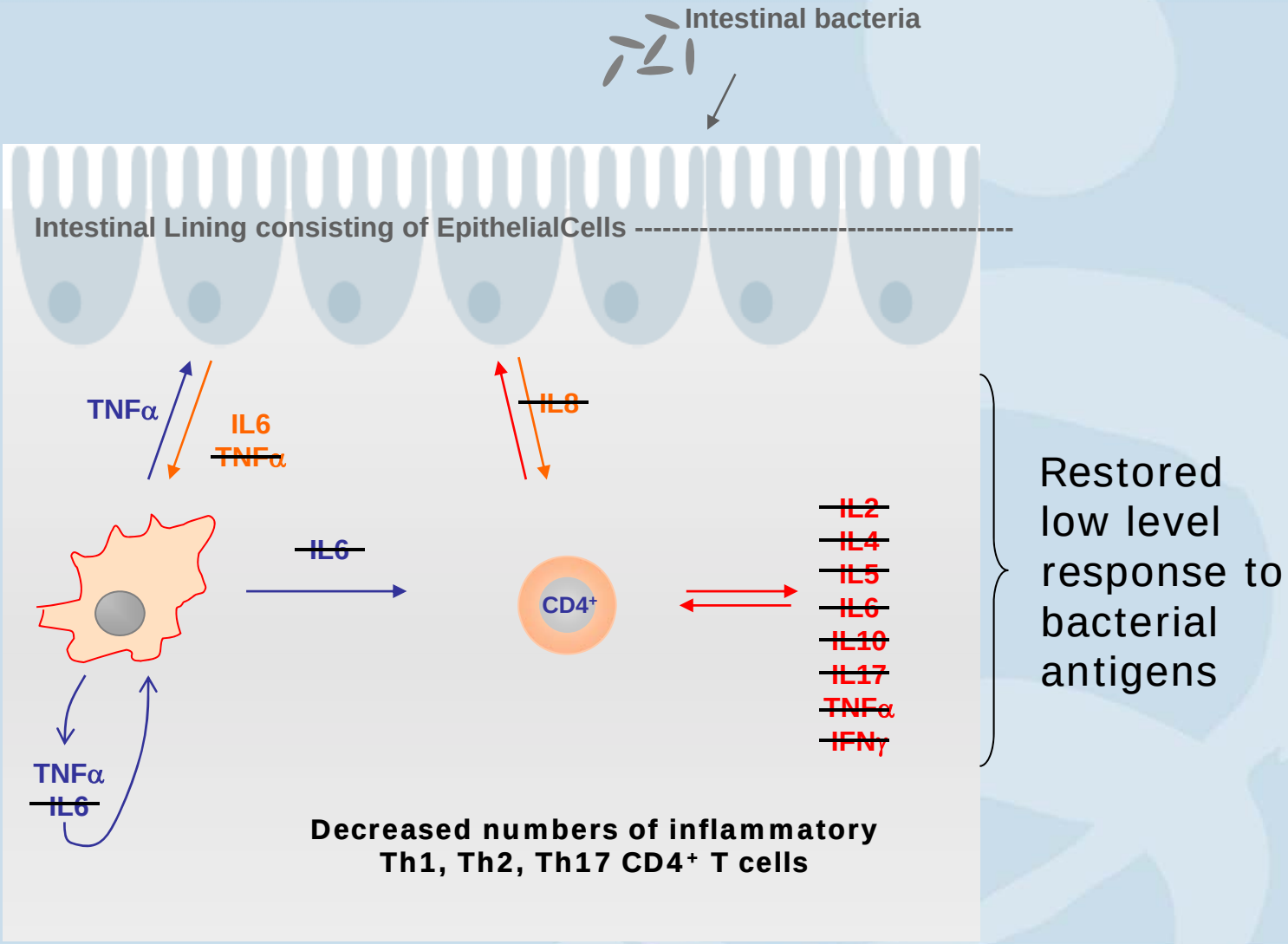
Cosmo's new business proposition for LMW Heparin

- **2 Cosmo drugs are targeted at induction of remission of mild to moderate UC**
  - Lialda
  - Budesonide MMX if approved
- **Long term studies indicate that ~50% of all patients will be in remission at any given time**
- **The market value for maintenance should be about 2/3 of the induction of remission market**

LMW Heparin inhibits the function and generation of inflammatory cells



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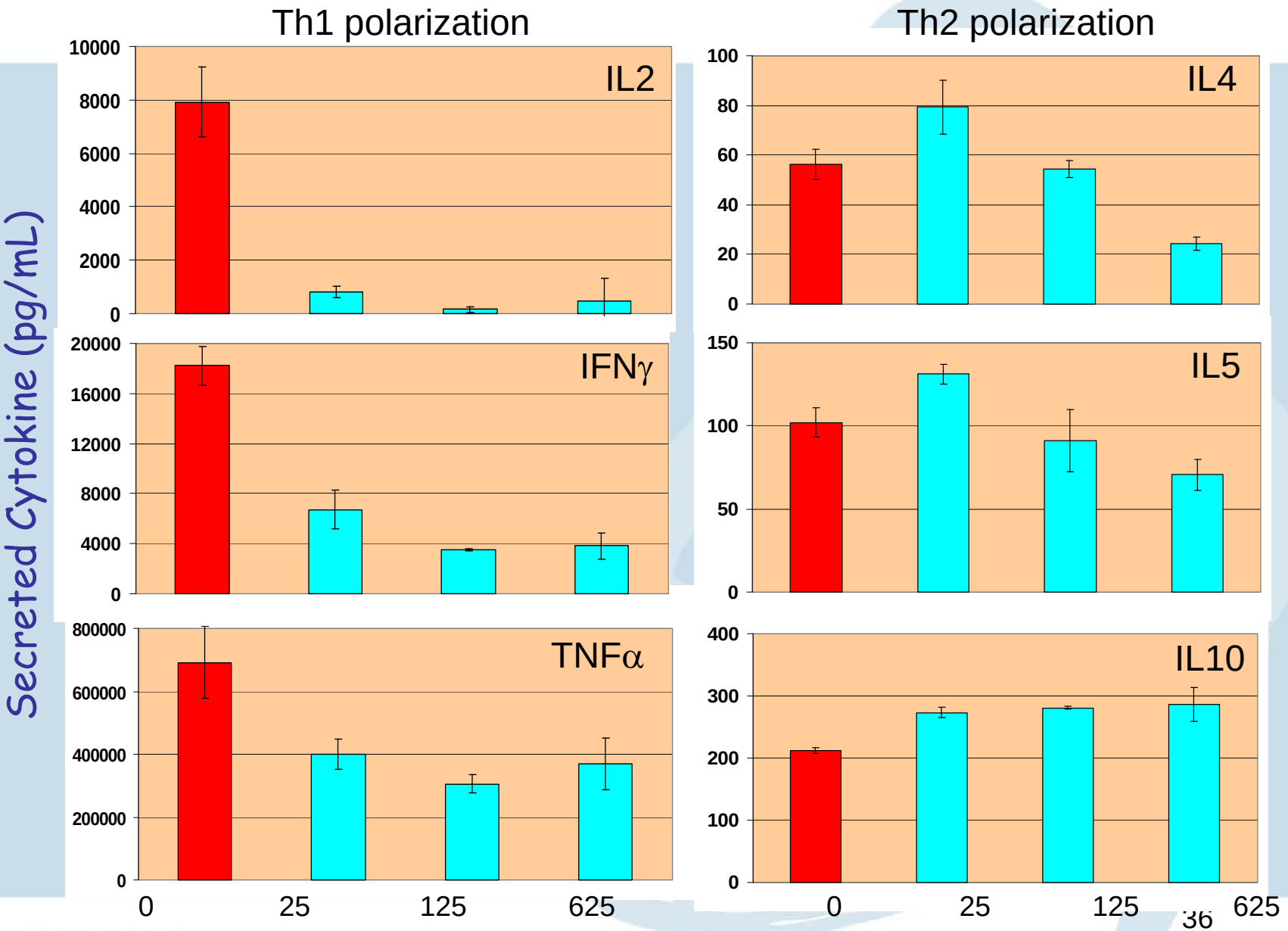
Parnaparin inhibits Th1 and Th2 polarization



(Courtesy of M. Gerloni)

LMW Heparin MMX®
indication in maintenance of remission

- **Completed phase IIb clinical trials; demonstrated that LMW Heparin MMX®, when associated to 5-ASAs**
  - Has no side effects
  - Stops bleeding and is substantially more effective than 5-ASAs

- **Possible target indication expanded to maintenance of remission for UC patients of all severity**
- New dose-ranging and POC study, designed as superiority vs. placebo, is planned
  - - 3 doses of drug + placebo
  - - 200 patients approximately
  - - 12 months of therapy
  - - patient eligibility: patients with history of UC mild to moderate severity coming in clinical remission (absence of blood in stools and absence of diarrhoea since at least one week) from whatever treatment
  - - maintenance criteria: absence of diarrhoea, absence of bleeding.
  - - quarterly evaluation visits

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LMW Heparin MMX®: indication in maintenance of remission

- **Pre-IND meeting with FDA results:**
  - LMW Heparin presently not approved in the USA, i.e. it is a new chemical entity
  - Full preclinical tests required including carcinogenesis tests

- **EU partnering discussions and discussions for phase III trial design planned in 2011**

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Cosmo's expanding business proposition

- **So far focus has been on Ulcerative Colitis, a disease that affects 1.7 m persons in the US and EU**

- **Next step has been to identify other areas where the MMX technology can be applied that are**
  - Larger
  - Can be accessed faster
  - Yet have low competition

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CB -01-16
Naloxone MMX

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CB-01-16: opioid antagonist MMX

- **Chemical entity:** *Naloxone*
- **Mechanism of action**
  - Naloxone is a powerful, off patent, opioid antagonist that displaces opioids from the cell receptor.
  - **Rationale**
    - Activation of opioid receptors present in the intestinal wall induces constipation. Specially affects long term users
    - 1 h plasma half life when administered parenterally, so the extended release formulations are needed
    - When taken orally, has a very high first pass effect being practically totally metabolized in the liver, without impairing analgesic effects
- **MMX application**
  - MMX technology brings Naloxone to the colon only where it displaces the opioid from their receptors thus restoring gut peristaltic movements

CB-01-16: opioid antagonist MMX

- **Market size**
  - In the US there are 12 m persons that are chronic opioid users and more than 4.5 m persons that suffer from chronic opioid induced constipation
  - Target is the home market
- **Status**
  - Phase I with dose escalation to start in H1 2011
- **Market need; competition**
  - Currently no tablet is approved for use
  - NKTR 119 uses Naloxol through pegilation technology. Licensed to AZ. In phase II

CB-01-16: opioid antagonist MMX

- **With 4.3 m persons with chronic constipation in the US alone this is a large market**
  - No treatments available for home use
- **Proof of concept can be achieved at low cost and fast**
  - Increasing dose Phase I will give quick indication whether peristaltic movement can be improved without pain increase
- **Poor experience of competitors**
  - a number of unsuccessful attempts at creating Naloxon based tablets have been made
- **New physician marketing base required**
  - Big marketing organization is required to market the drug

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CB-17-01
Methylene Blue MMX

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Worldwide variation in colorectal cancer mortality rate (cases per 100.000)

> 33.5/100.000

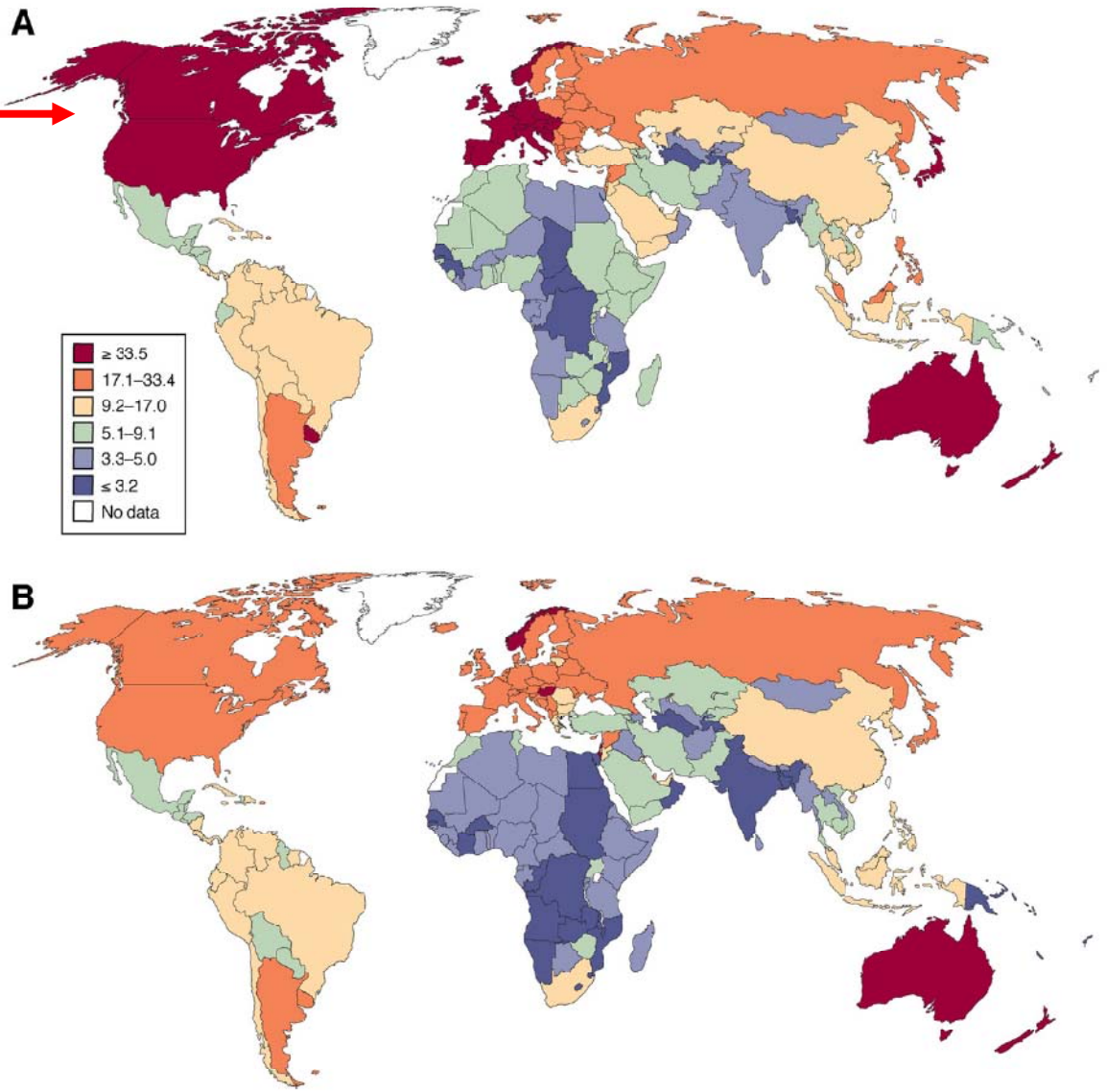

Figure 5. Worldwide variation in colorectal cancer mortality rates (cases per 100,000) in (*A*) male subjects and (*B*) female subjects. Adapted from Ferlay J, Bray F, Pisani P, et al. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase no. 5, version 2.0. Lyon, France: IARCPress, 2004.

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Costs of colorectal cancers

Table 1. Estimates of National Direct Medical Expenditures for Cancer Treatment in 2004 US Dollars

	Percentage of all new cancers (1998)	Expenditures (billions of dollars)	Percentage of all cancer treatment expenditures
Lung	12.7	9.6	13.3
Colorectal	10.7	8.4	11.7
Breast	15.9	8.1	11.2
Prostate	16.8	8.0	11.1
Lymphoma	4.6	4.6	6.3
Head/neck	2.8	3.2	4.4
Bladder	4.4	2.9	4.0
Leukemia	2.4	2.6	3.7
Ovary	1.9	2.2	3.1
Kidney	2.6	1.9	2.7
Endometrial	2.9	1.8	2.5
Cervix	0.8	1.7	2.4
Pancreas	2.3	1.5	2.1
Melanoma	4.0	1.5	2.0
Esophagus	1.0	0.8	1.1
All other	14.0	13.4	18.5
Total	100.0	72.1	100

NOTE. Costs are based on cancer prevalence in 1998 and cancer-specific costs for 1997 to 1999 projected to 2004 using the medical care component of the Consumer Price Index. Adapted from National Cancer Institute.[8]

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Colorectal cancer screening program

- Colorectal cancer is the third leading cause of death for tumors in western countries
- It develops through a precursor (polyp) which can be identified and removed during colonoscopy
- The core goal of colonoscopy is to detect all premalignant polyps, primarily adenomas, and remove them completely
- All western countries have largely adopted nationwide screening programs with FOBT or colonoscopy to reduce the incidence of colorectal cancer

Colonoscopy in colorectal screening program

- **Observational studies show that colonoscopy-based screening programs have resulted in:**

  - ***earlier detection of cancer***

    Hoff G, et al BMJ 2009, Gross CP JAMA 2006

  - ***decreased incidence of colorectal cancer***

    Brenner H, Eur J Cancer 2009, Kahi CJ, Clin Gast Hep 2009

  - ***decreased mortality from colorectal cancer***

    Baxter NN, Ann Intern Med 2009

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But Colonoscopy is an imperfect diagnostic tool

- **Population based studies suggest that 2% to 6% of prevalent cancers are missed by colonoscopy**
- **Adenoma missing rate is around 15-20%**
- **Colonoscopy miss rate may be higher for lesions in the proximal colon**
- **Colonoscopy miss rate may be higher for flat lesions and for those smaller than 10 mm**

Bressler B, Gastroenterology 2007

Farrar WD, Clin Gastroenterol Hepatol 20

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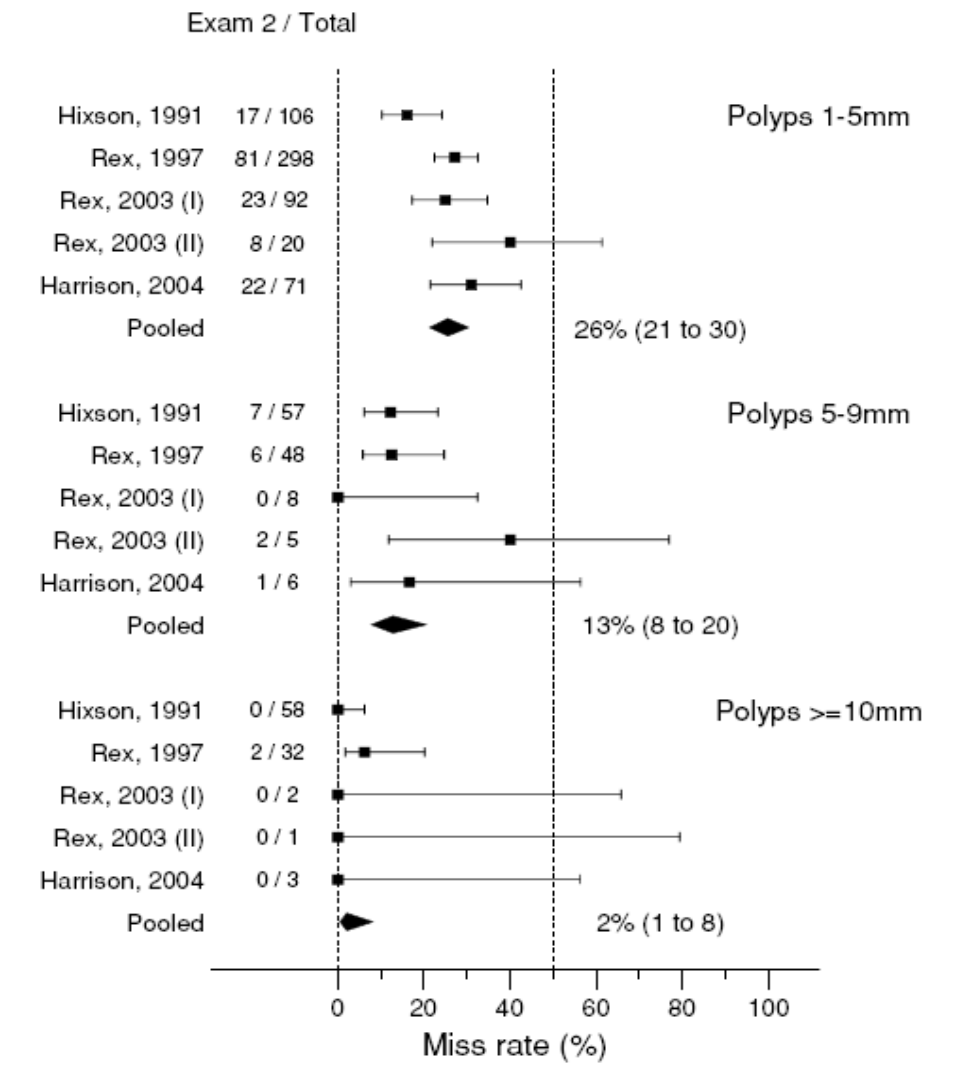
Polyp miss rate determined by tandem colonoscopy: a Review



van Rijn JC. Am J Gastroenterol 2006

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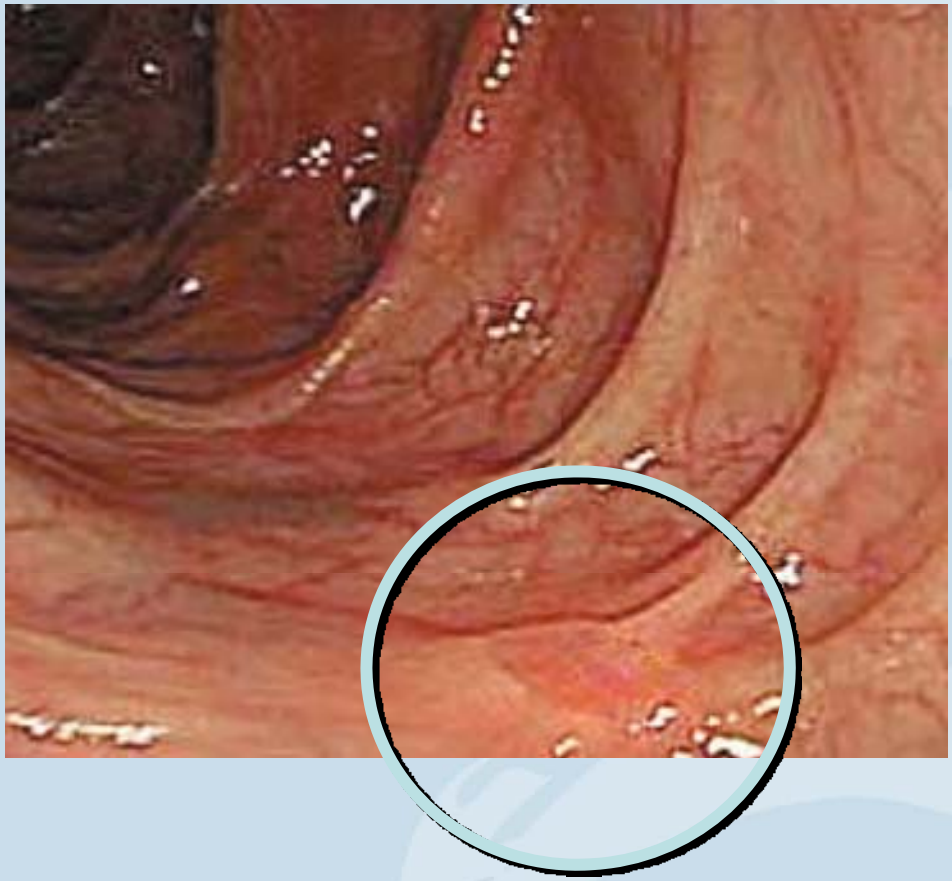
Flat and Depressed Lesions are challenging to be identified



The Paris endoscopic classification of superficial neoplastic lesions
Gastrointest Endosc 2003

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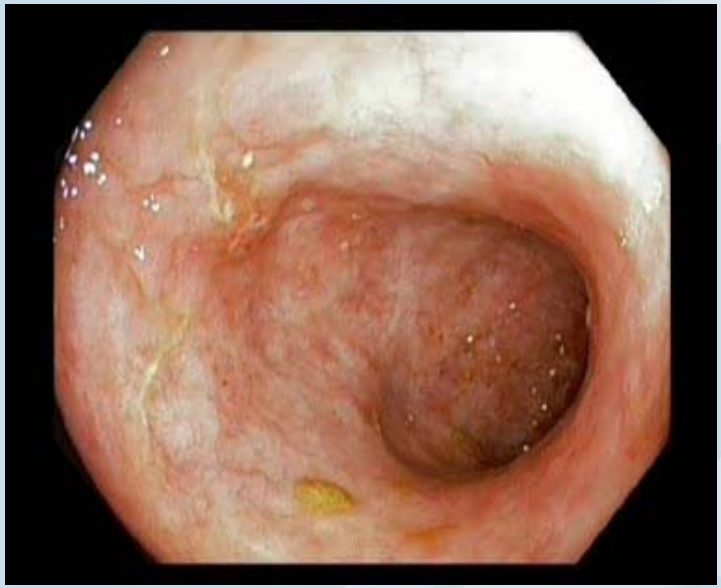
Longstanding UC

- **Neoplasia in longstanding UC frequently develops in flat and non-suspicious appearing mucosa**



Ransohoff DF. Dis Colon Rectum 1985
Rubin CE. Gastroenterology 1992
Tytgat GN. Eur J Cancer 1995
Eaden JA. Gut 2001
Rutter M. Endoscopy 2004

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Polyp detection rate

- In expert hands and with ancillary techniques (chromoendoscopy, NBI, etc) should be around 50% in patients older than 50 y
- Appropriate detection impacts: therapeutic management, risk stratification for cancer and follow-up programs
- Improper detection significantly increases costs management for the single patients and the health system

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What is our goal

- **See more**
- **See better**
- **Differentiate: Adenoma *vs* hyperplastic**
- **Differentiate: Advanced *vs* early**

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The concept of chromoendoscopy for colonoscopy

- In chromoendoscopy, intravital dyes like methylene blue are topically applied onto the mucosal surface
- The aim is to enhance superficial patterns and contrast of pathologic versus normal mucosa
- This relatively old technique can be used in an untargeted fashion ("panchromoendoscopy") to increase detection of lesions
- Alternatively can be used in a targeted mode to define the borders of the lesions and their pattern (adenoma *vs* hyperplastic or adenoma *vs* carcinoma)

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Methylene Blue dye (0,5%)

It's selectively absorbed by the normal colonic columnar cells

No uptake by the dysplastic or neoplastic cells

Increases the visibility of the structure because of the color itself

Regular colonic mucosa → Homogeneous diffusion

Dysplasia Neoplasia → Non-colored area or scarcely colored

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Why Methylene Blue?

- Easily available for pharma use
- Long tradition as dye for foods
- Large number of studies on toxicity
- Long tradition in digestive endoscopy (> 20 y)
- Probably the most largest used dye in endoscopy worldwide

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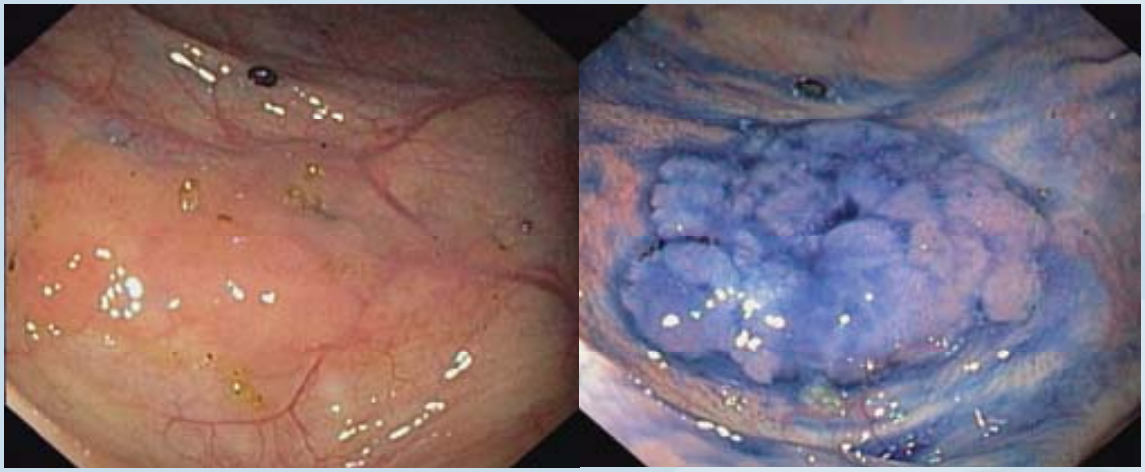
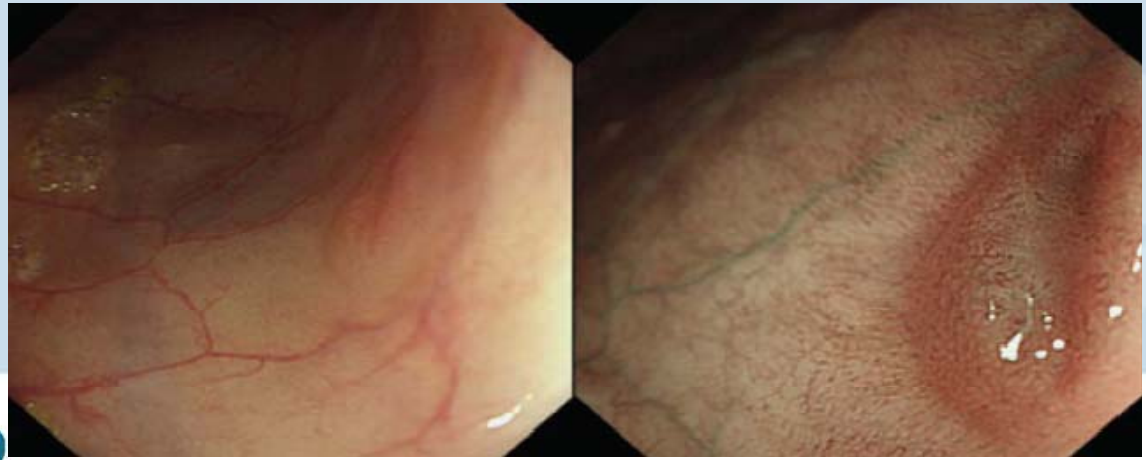


Narrow Band Imaging



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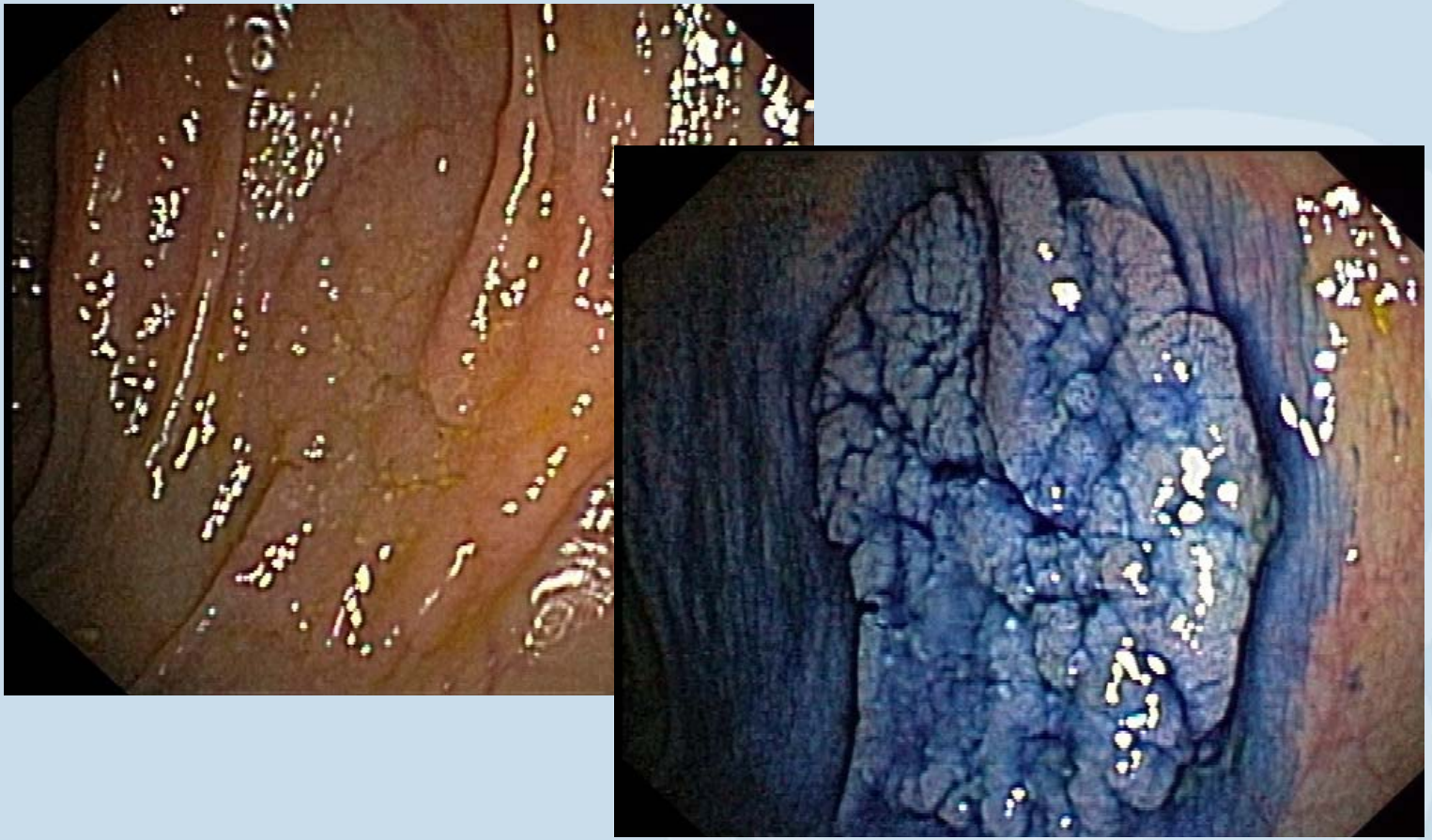
Chromoendoscopy

Old Technique (’70s)
Developed by Japanese Experts



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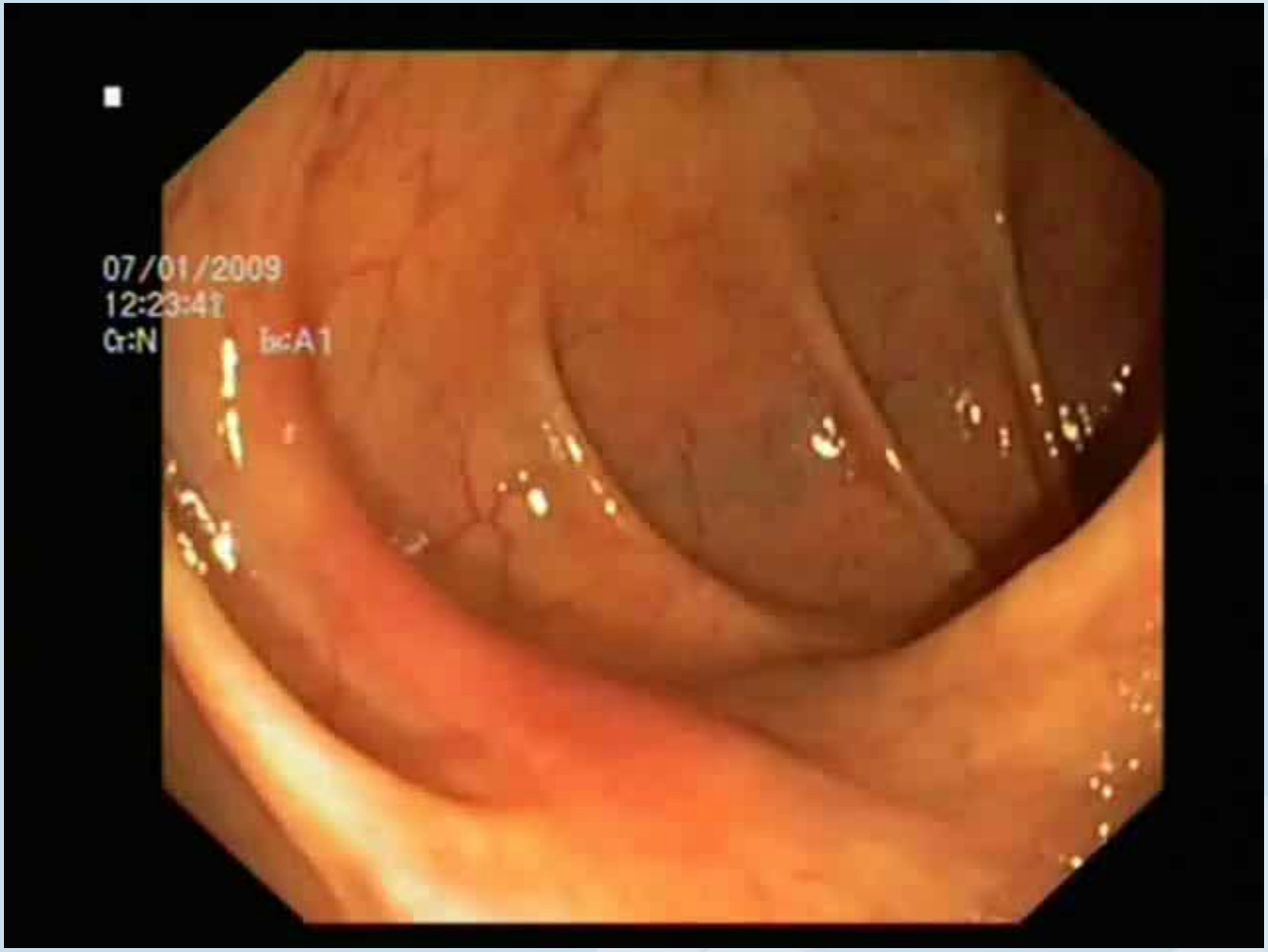
Chromoendoscopy with methylene blue



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Adenoma Detection Rate

260 patients randomized to CE or SC

Histology	Control Group	Chromoscopy	p
Hyperplastic	45	72	p<0.001
Adenoma LGD	49	89	p<0.05
HGD / K insitu	9	23	

Significant (P < 0.05) increase in the detection of adenomas (112 vs. 57), without a difference in extubation times (17 vs. 15 min; P > 0.1)

What happens in real life with chromoendoscopy

- Time-consuming
- Boring
- Dye diffusion is not homogeneous
- Learning curve / standardization
- Culture / education / training / nurses

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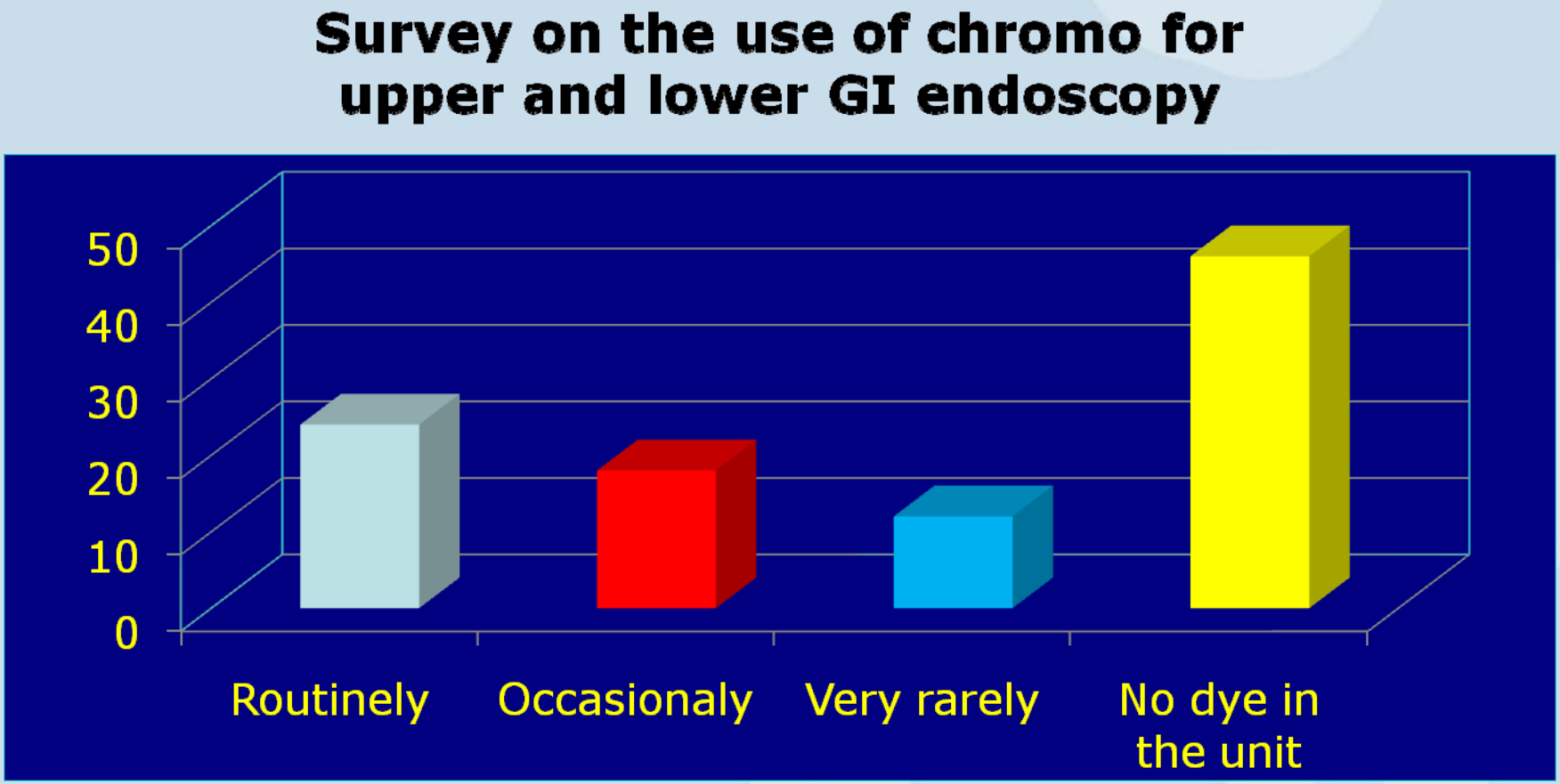
Italian survey on chromoendoscopy



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Why the use of dye is still scarcely adopted in Western Countries?

- Dye purchase and storage difficulties
- Dye preparation-dilution
- Dirty technique
- It takes pre-colonoscopy time and efforts (costs)
- It takes time if a “pan-chromo-colonoscopy” is required

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MMX released methylene blue

- Revolutionary concept
- Easy and smart way to by-pass a number of issues precluding large-scale adoption of chromoendoscopy
- MMX tablets containing methylene blue
- MMX technology targets release of the dye at colonic level
- Pre-colonoscopy dyeing of the mucosa
- No interference with standard bowel prep

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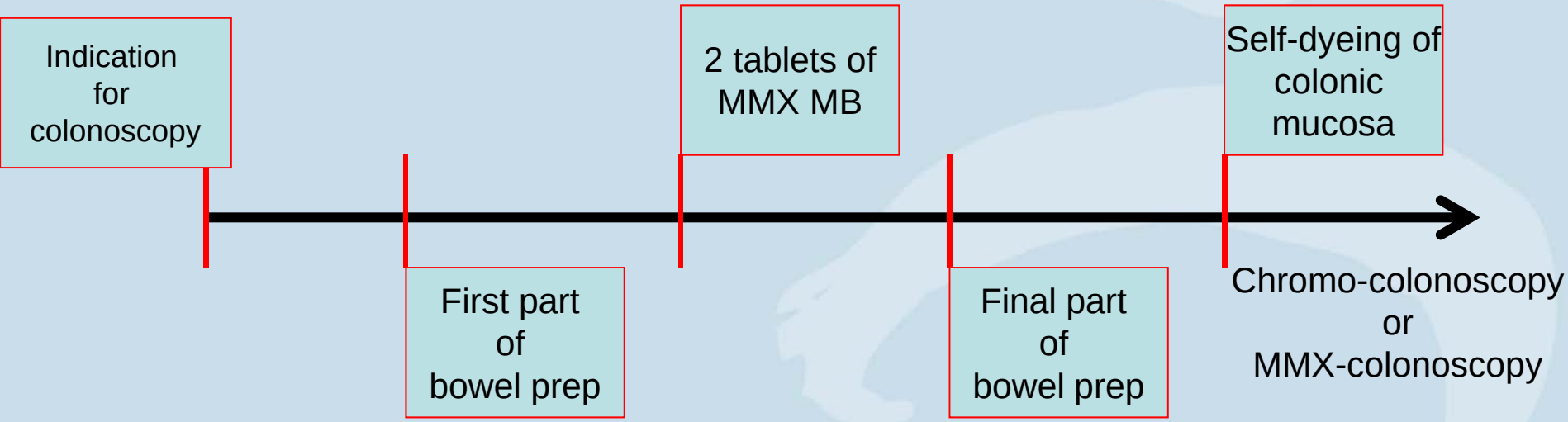
The future of colonoscopy



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CB-17-01: Methylene Blue MMX business rationale

- **With 15 m colonoscopies in the US alone and > 30 m WW this is a very large market**
  - The market potential is as high as all colonoscopies
- **Great leeway in pricing**
  - Using the Methylene Blue tablet decreases time of colonoscopy by up to 50% vs classical chromoendoscopy
- **Inexpensive and fast to develop**
  - Proof of concept attained, major hurdle of PK study successfully completed
  - Clinical trials are fast, market entry targeted for end 2013
- **New application with no competition in sight**

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- **Anti Androgen**

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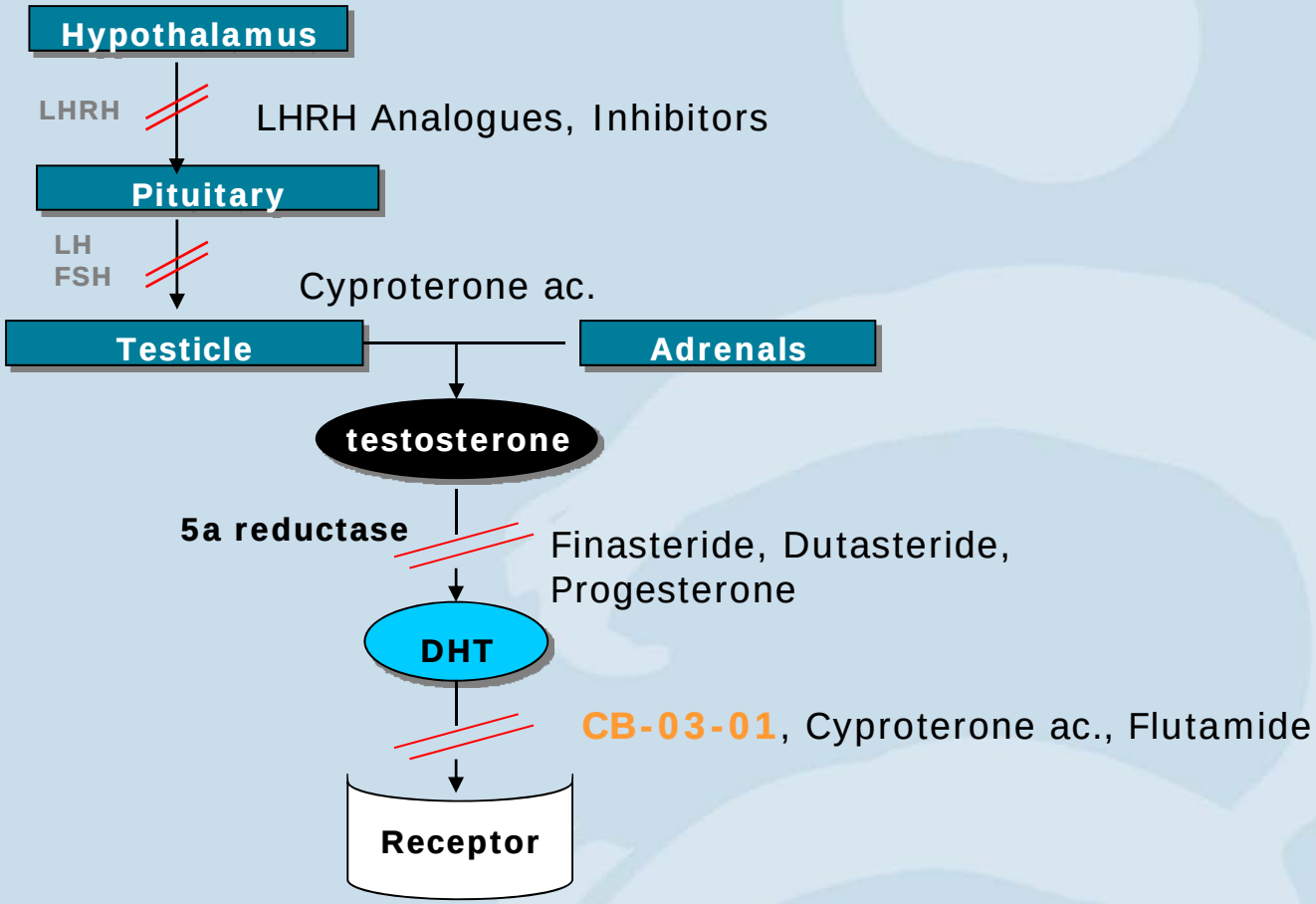
CB-03-01: Anti-androgen for topical applications

- **Chemical name**
  - *Cortexolone 17α-propionate*
- **Therapeutic Area** *Antiandrogenic (ATC D11 AX)*
  - New Chemical Entity (NCE) with antiandrogen properties, under development for topical treatment
  - Anti-androgen without systemic effects
  - Acts only at the level of the skin androgen receptor, blocking the binding or displacing androgen hormones to the sebaceous gland and to the hair follicle; additionally it has moderate anti inflammatory activity
- **Medical need**
  - A treatment for acne, sebborhea, alopecia and hirsutism that is effective by topical application
  - A topical treatment that provides a reliable alternative to retinoids (poorly tolerated and presence of side-effects) and antibiotics/anti-infectives
  - Is not a skin irritant
  - Due to its peripheral effects, it does not induce hormonal imbalance

Endocrine control of androgen-dependent organs, and mechanism of action



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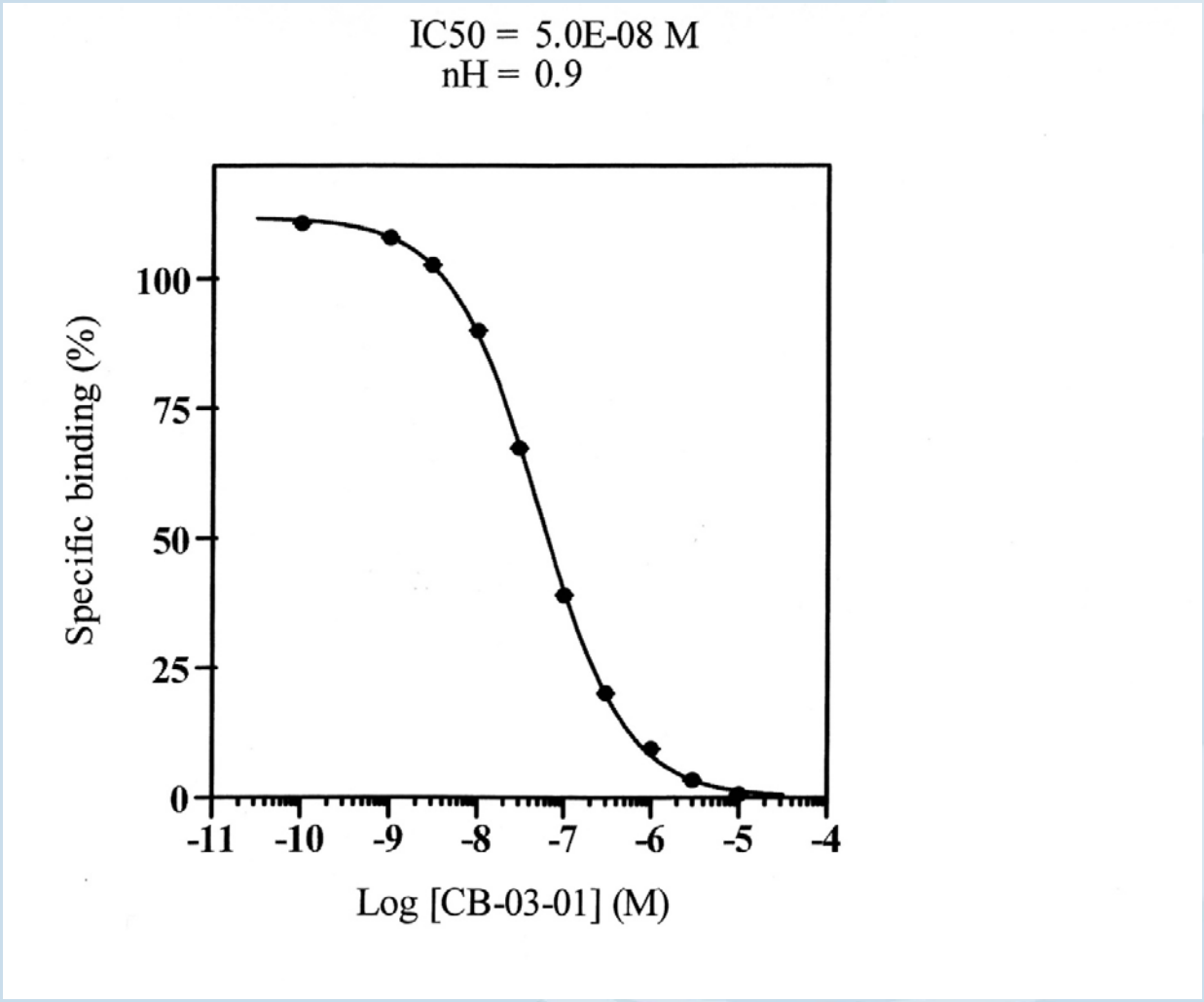
CB-03-01 has substantially stronger cell receptor binding than Testosterone or DHT

Competitive curve at the LNCaP human androgen receptor



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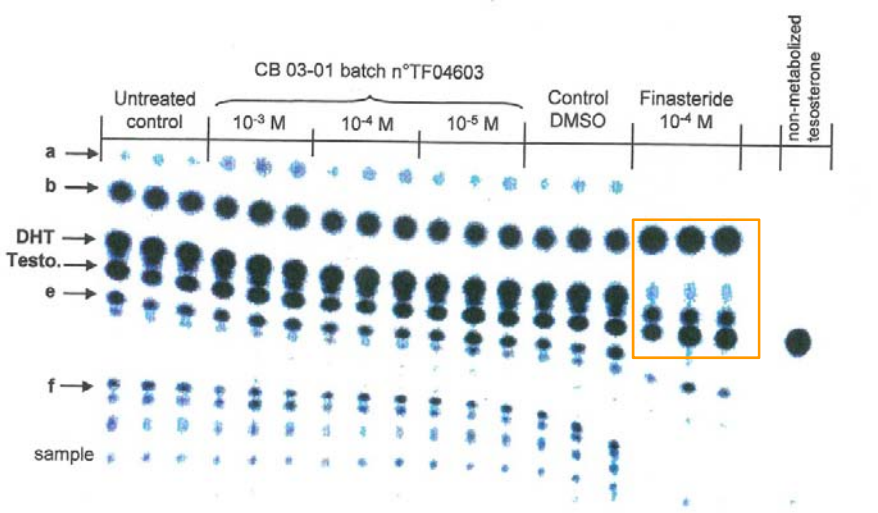
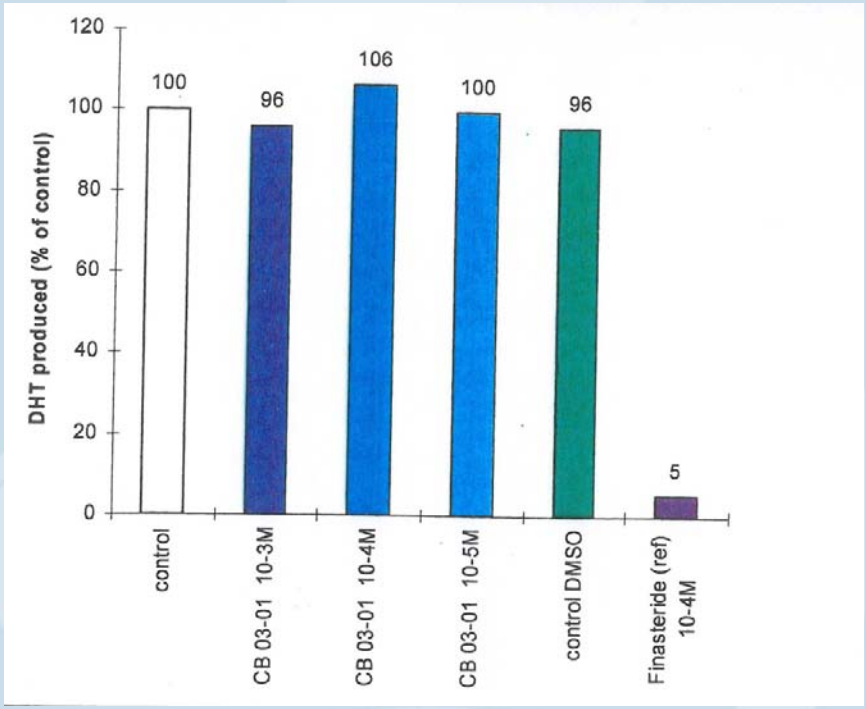
CB-03-01: does not inhibit 5 α-reductase nor influence skin metabolism of testosterone to DHT

[^{14}C]-testosterone and metabolites after transepidermal diffusion (24h)
Thin layer chromatography and autoradiography



a: 5α-androstane-3,17-dione, b: 4-androstene-3,17-dione, Testo:testosterone, DHT: 5-dihydrotestosterone, e & f: polar metabolites



Unlike finasteride, CB-03-01 does not inhibit skin 5α-reductase, and does not influence skin
metabolism of testosterone to DHT

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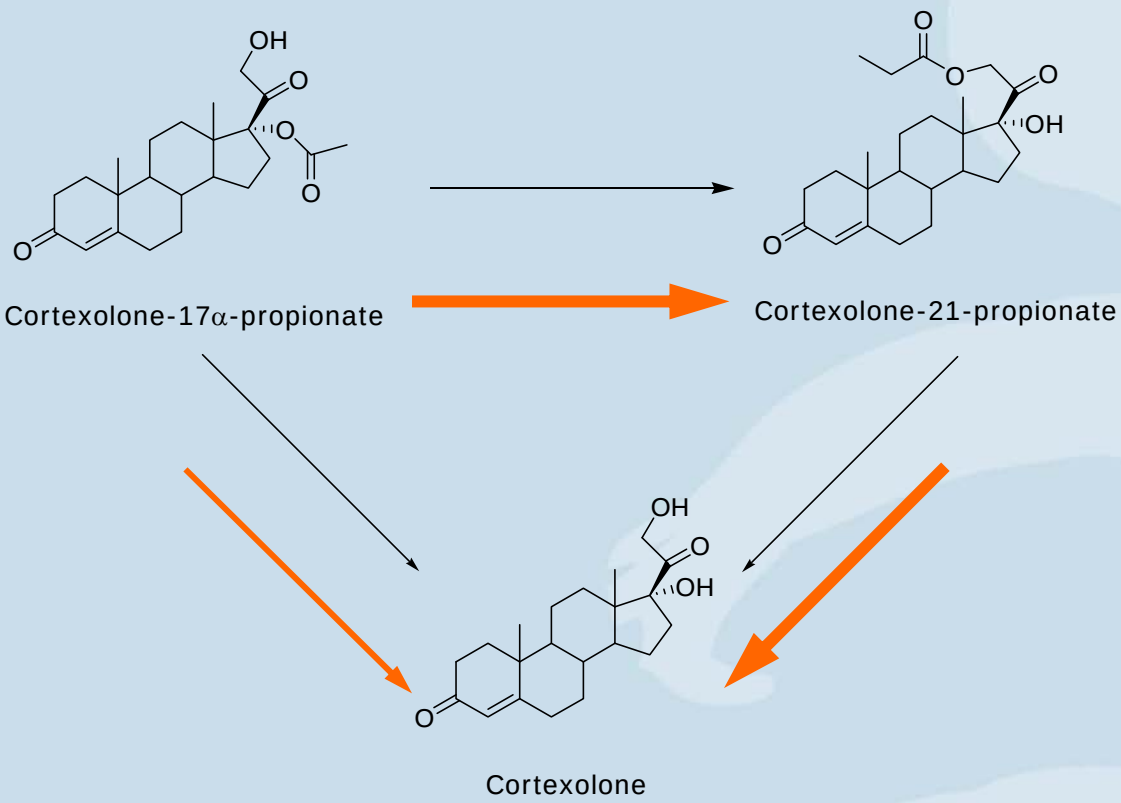
CB-03-01: has a very simple and linear metabolic pathway and metabolizes to safe cortexolone



- **The final compound is cortexolone, whose safety profile is well known**
- **The aim is to achieve high local activity together with systemic safety thanks to the in vivo hydrolysis pattern**

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CB-03-01: penetrates human skin better than competitors

Penetration/permeation of test compounds using human skin in vitro

Compound	Solution [a]	Concentration [%]	Skin concentration [µg/g]	Permeation rate [ng/ml/hr]
Cyproterone acetate (CA)	PG	0.73	12.3 ± 3.7	not detectable [b]
	PG/OL	0.94	89.4 ± 4.6	141 ± 17
CB-03-01	PG	0.92	36 ± 8 (1 ± 0.2) [c]	7 ± 0.4
	PG/OL	0.99	231 ± 19 (44 ± 5) [c]	1410 ± 137

[a] PG: propylene glycol, PG/OL: propylene glycol/oleyl alcohol 9:1

[b] Limit of quantification: approx. 2 ng/ml/hr

[c] Values in parentheses: levels of cortexolone in the skin at 48 hours

Skin concentration and permeation of CB-03-01 in PG/OL resulted about 2.5 and 10 times higher than those of Cyproterone acetate

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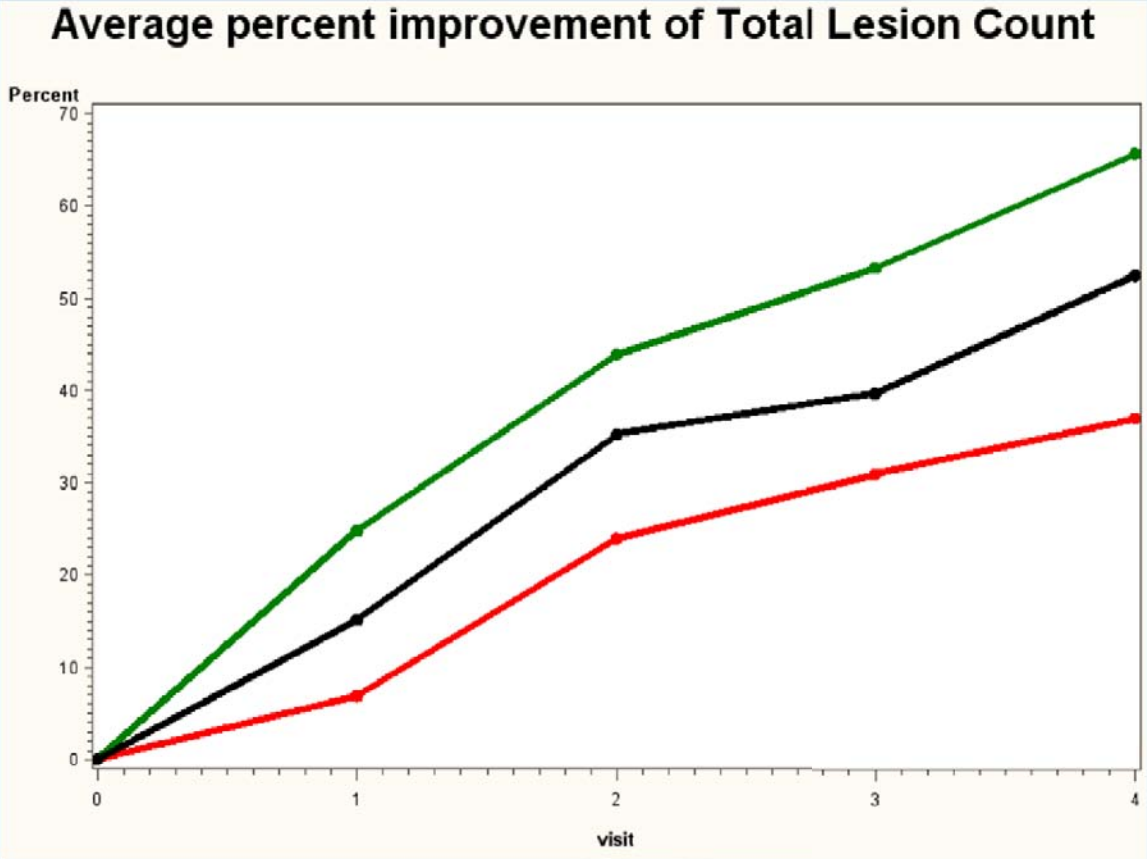
CB-03-01
Clinical development and opportunities

- **Status**
  - Phase I studies in volunteers successfully completed
    - Product well tolerated
    - No measurable side effects
    - Drug permeates skin and is quantifiable in plasma (syst. abs <1%)
  - Phase II proof of concept study on 72 patients with acne vulgaris [2009]
    - Comparison to Retin-A and Placebo
    - Study completed
    - CB-03-01 statistically and/or clinically more effective than Placebo and comparator
    - CB-03-01 rapid onset of activity
    - CB-03-01 very well tolerated
- **Opportunities**
  - First topically effective anti-androgen treatment in the market

CB-03-01 1% cream
Phase II Study – Clinical Results



CB-03-01 1% cream

Retin-A 0.05 % cream

Placebo

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CB-03-01 1% cream
Phase II Acne Study Clinical Results - Summary

Efficacy of CB-03-01 1% cream in acne vulgaris

Parameter	Placebo cream (n=14)	Retin-A 0.05% cream (n=30)	CB-03-01 1% cream (n=28)
Total Lesion Count (TLC)			
- % reduction vs. baseline, at weeks 8	37.1	52.5	65.7 [(a)]
- median time (days) to reach improvement 50%	58	57	43
Inflammatory Lesion Count (ILC)			
- % reduction vs. baseline, at weeks 8	38.9	50.7	67.2 [(b)]
- median time (days) to reach improvement 50%	58	44	36
Acne Severity Index (ASI)			
- % reduction vs. baseline, at weeks 8	39.5	53.0	68.3 [(c)]
- median time (days) to reach improvement 50%	57	44	42
Investigator Global Assessment (IGA)			
- % of success at weeks 8	7.1	11.5	22.2

[(a)] statistically significant vs. Placebo (<0.001) and vs. comparator (<0.05)
[(b)] statistically significant vs. Placebo (<0.05)
[(c)] statistically significant vs. Placebo (<0.01)

CB-03-01 Phase I clinical development (I)

Pharmacokinetic of repeated doses

Study Design: Multiple dose, placebo-controlled, cutaneous tolerability and pharmacokinetic in adult healthy volunteers

Subjects: 24 volunteers of both sexes

Treatment: CB-03-01 1% cream applied to fixed dorsal skin area at volume of 4 mL and 8 mL for 14 days; Placebo cream applied to the control lateral side

Assessment: Local and systemic tolerability;
Determination of plasma concentration of CB-03-01 and free cortexolone, and urinary excretion of CB-03-01, cortexolone and tetrahydrocortexolone after 1st, 10th and 14th applications

Status: Completed

Results: CB-03-01 1% cream was very well tolerated;
CB-03-01 was absorbed in blood stream in a proportion < 1% of the applied dose;
absorption and urinary excretion were not proportional to the volume applied

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CB-03-01 Preclinical Development

Materno-foetal toxicity in rat and rabbit

Treatment:

- ***Rat:*** Subcutaneous, daily doses 0, 1, 5, 25 mg/Kg b.wt
- ***Rabbit:*** Subcutaneous, daily doses 0, 0.1, 0.4, 1.5 mg/Kg b.wt

Status: Completed

Results: No evidences that CB-03-01, at the tested doses, presented unexpected materno-foetal toxicity in animals

CB-03-01 Phase I development : Skin irritation in man

Study Design: Multiple dose, randomized, positively and negatively controlled study

Subjects: 36 adults healthy volunteers of both sexes

Treatment: CB-03-01 1% cream (0.2 mL), laurylsulfate 0.2% (0.2 mL) [positive control], white petrolatum cream (0.2mL) [negative control] daily applied for 15 days (22 days of exposure) to the dorsal skin

Evaluation: Skin irritation index

Status: study ongoing (Final report planned: Feb 2011)

Planned an IND with FDA for clinical development in the USA

CB-03-01 in Androgenetic Alopecia (AGA)
Overview from a clinical, ambulatory experience (I)

Aim:	To evaluate the efficacy and safety of CB-03-01 1% and 5%, compared to Cyproterone acetate and 17α-estradiol applied by hydroelectrophoresis to scalp of subjects affected by AGA
Design:	Single-centre, open-label, not randomized, four parallel groups evaluation
Subjects:	40 males affected by AGA (Hamilton grade I-IV) 30 females of no child-bearing potential affected by AGA (Ludwig grade I) All subjects in good general conditions, not receiving AGA treatments in previous 6 months, and signing informed consent form
Products:	CB-03-01 1% (males & females) CB-03-01 5% (males & females) Cyproterone acetate 1% (only females) 17α-estradiol 1% (only males)
Treatment:	Test items dispersed in a specific gel for hydroelectrophoresis, and applied to the scalp by hydroelectrophoretic technique. Applications occurred once or twice a week, for five sessions of about 20 minutes each
Assessments:	
Clinical evaluation	Hair shaft diameter, Pull test, Wash test, Follicular density, Sebometric evaluation, Proportion of subjects improved
Confocal Microscopy	Sebaceous gland size, Fibrosis evaluation, and Peribulbar inflammation
Timing	Evaluation performed at baseline, and 1 and 4 weeks after completion of treatment

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CB-03-01 in Androgenetic Alopecia (AGA)
AN OVERVIEW FROM AN AMBULATORY EXPERIENCE (I)

RESULTS OF CLINICAL DATA:

Parameter	CB-03-01 1%			CB-03-01 5%			Cyproterone ac. 1%			17α-estradiol 1%		
	Basal	*T1*	*T2*	*Basal*	*T1*	*T2*	*Basal*	*T1*	*T2*	*Basal*	*T1*	*T2*
Hair diameter (mm)	0.41	0.73	0.88	0.66	0.74	0.91	0.51	0.61	0.74	0.53	0.65	0.73
Pull test (score)	3	1	1	3	1	1	3	2	2	3	1	1
Wash test (hairs n°)	181	123	64	193	117	65	178	132	72	196	136	71
Follicular density (n° / cm²)	71	89	109	73	88	111	70	82	96	74	84	98
Sebometric evaluation (qualitative)	high	medium	low	high	medium	low	high	medium	low	high	high	high
Subjects improved (%)	---	76	85	---	79	85	---	59	66	---	61	69

T1 = one week after treatment completion; ***T2*** = four weeks after treatment completion

OVERALL:

CB-03-01 at both concentrations 1% and 5% consistently increased hair diameter, follicular density and overall improvement more than Cyproterone acetate 1% and 17α-estradiol 1%

CB-03-01 was also more active than comparators in improving pull test, wash test and sebometric evaluation

No evident difference of activity detected between the two concentrations of CB-03-01

No local or systemic effects were reported following the administration of the tested items

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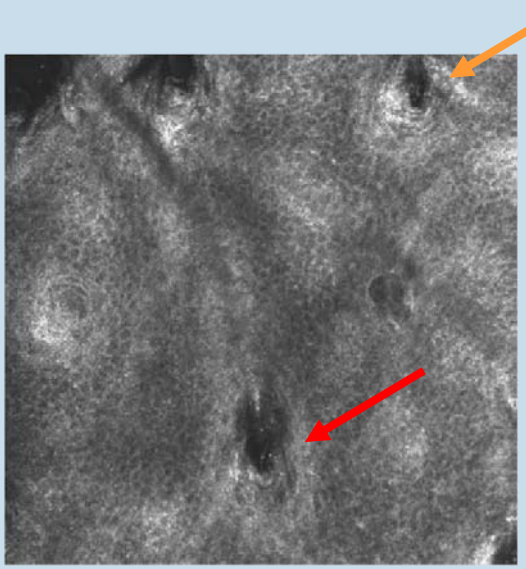
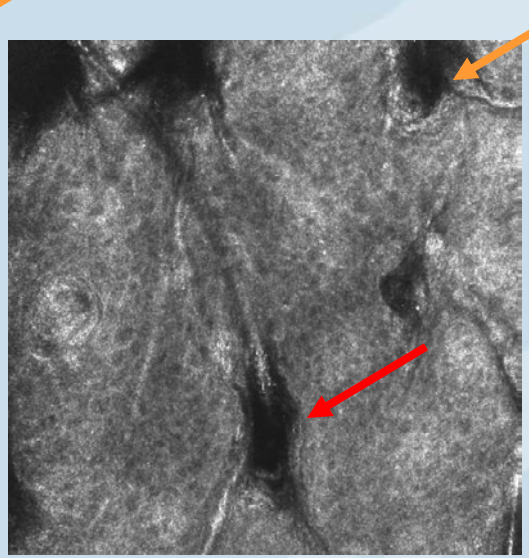
CB-03-01 in Androgenetic Alopecia (AGA)
AN OVERVIEW FROM AN AMBULATORY EXPERIENCE (III)

RESULTS OF CONFOCAL MICROSCOPY

The technique highlighted:

- an increase in the **shaft diameter**, mainly evident in CB-03-01 groups, as reported in clinical data table
- an impressive reduction of **sebacious gland size**, observed in about 85% of treated subjects.
- a decrease in **dermal fibrosis**, indicator of inflammatory process, after treatment mainly with CB-03-01
- a reduction of **vessel diameter** of peribulbar microvasculature
- a reduction of **inflammatory cells** after treatment with CB-03-01.





left) a follicular ostium partially obstructed by the edges of the sebaceous gland.

right) after the treatment with cortex -17α-propionate 1%, the calibre of the follicular ostium has increased after a decrease in the dimension of the sebaceous gland (150μm)

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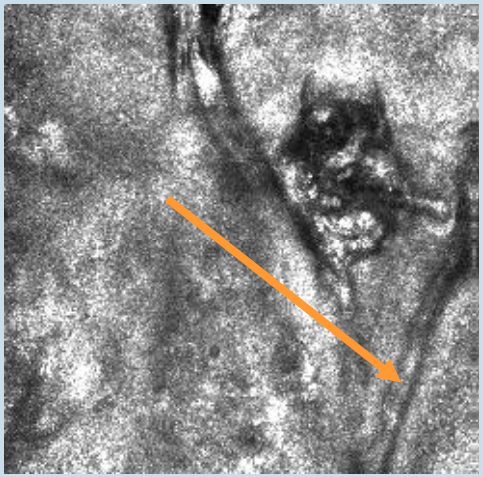
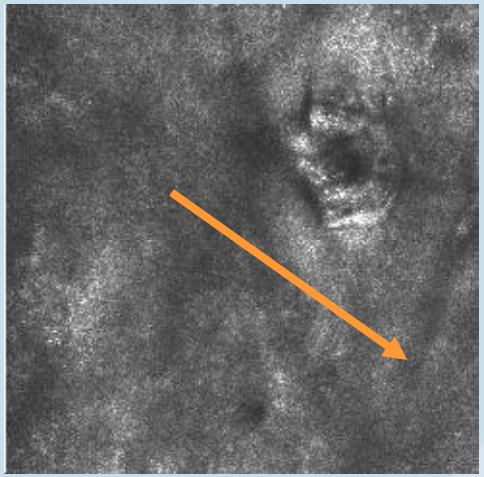
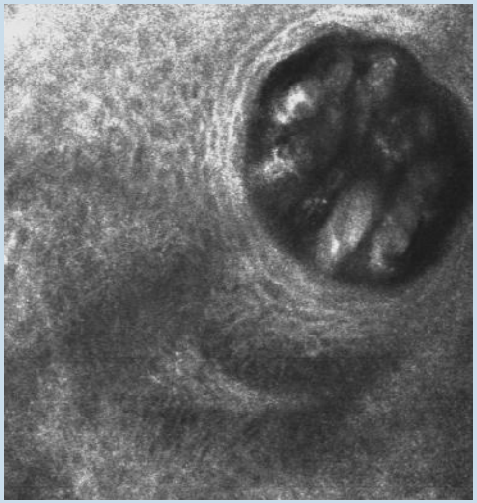
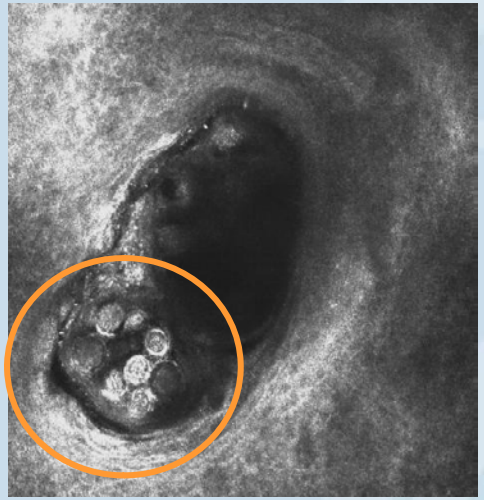
CB-03-01 in Androgenetic Alopecia (AGA)
AN OVERVIEW FROM AN AMBULATORY EXPERIENCE (II)





Reduction of vessel diameter of peribulbar capillaries and a decrease of the number of inflammatory cells was noted after treatment with CB-03-01





From left to right:
- reduction of dimension of sebaceous gland
- improvement of the follicolar units inside the ostium (5 hair follicles)
- reduction of inflammatory and fibrotic evidence around the ostium

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CB-03-01
Patents overview

Two patents have been filed, covering:

- the new molecular entities family and its application as antiandrogenic compounds

  EP 1421099
  granted 2005 in **EU, AUS, CHI, JP,CAN, KR, MEX, IN**, pending **USA**

- the specific crystalline forms obtained with the different synthetic processes

  PCT/EP2008/059072
  pending approval in **EU, AUS, CHI, JP,CAN, KR, MEX, IN, RU, USA, ZA**

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CB 03-01: alopecia Business rationale

Market potential

- It is presumed that around 40% of men between 20 and 65 suffer hair loss and up to 40% of these try to do something about it
    - **Around 20% of these are willing to use drugs ie around 3% of all men**
- Up to 50% of all women after menopause suffer hair loss and up to 60% of these try to do something about it
    - **Around 33% of these are willing to use drugs , ie around 10% of all women>50**

FDA approved drugs

- No topical anti androgen approved
- Propecia; an alpha 5 reductase inhibitor, taken as a tablet, had revenues of $ 429 m (2008)
- Minoxidil/Regaine/Rogaine are vasodilators and are off patent

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Outlook for 2011

- **Continued growth in Lialda revenues by > 20%**
- **Growth of contract drug and generic manufacturing by>10%**
- **Licensing agreements for CB 03-01 and LMW Heparin**
- **Slight increase in SG&A**
- **External R&D costs**
  - Anti Androgen EUR 1.5 m
  - Blue Methylene EUR 1.0 m
  - Opioid Constipation EUR 0.5 m

COSMO Pharmaceuticals

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