

R&D Day

Lainate

January 19, 2012



Safe harbor

This presentation may include forward-looking statements that are based on our management's beliefs and assumptions and on information currently available to our management.

The inclusion of forward-looking statements should not be regarded as a representation by Cosmo that any of its plans will be achieved. Actual results may differ materially from those set forth in this presentation due to the risks and uncertainties inherent in Cosmo's ability to develop and expand its business, successfully complete development of its current product candidates and current and future collaborations for the development and commercialisation of its product candidates and reduce costs (including staff costs), the market for drugs to treat IBD diseases, Cosmo's anticipated future revenues, capital expenditures and financial resources and other similar statements, may be "forward-looking" and as such involve risks and uncertainties and risks related to the collaboration between Partners and Cosmo, including the potential for delays in the development programs for Budesonide MMX® and Rifamycin SV MMX®. No assurance can be given that the results anticipated in such forward looking statements will occur. Actual events or results may differ materially from Cosmo's expectations due to factors which include, but are not limited to, increased competition, Cosmo's ability to finance expansion plans, the results of Cosmo's research and development activities, the success of Cosmo's products, regulatory, legislative and judicial developments or changes in market and/or overall economic conditions. Cosmo assumes no responsibility to update forward-looking statements or to adapt them to future events or developments.

You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof, and Cosmo undertakes no obligation to revise or update this presentation.

Program

- 11:00** **Welcome**
Update on Lialda
Update on Budesonide MMX
Update on Rifamycin SV MMX
Update on Methylene Blue MMX
Coffee break
Update on CB-03-01
Update on other programs
Closing words
- 13:30** **Lunch**
- Visit of MMX manufacturing plant**

Evolution of Cosmo

- **Cosmo from 1997 to 2011**

- Went from 40 employees about to be fired to around 160 employees
- Have two products in the market and 3 products within ~24 months of market entry
- Have generated high colon expertise
- Have one of most comprehensive IBD portfolios in the industry
- Have a very low cost in developing products
- Have been consistently profitable

How was this success created?

- **Cosmo is an Italian success story**
 - Deep sense of belonging of team
 - Knows its strengths and builds on these
 - Senior management knows the entire business
 - Can move fast
 - MMX technology is functional and elegant
 - Is not financially dependent on others

Update on Lialda®

- **Shire 2011 revenues ~ \$ 380 m and peak sales UC expected at ~ \$ 550 m**
 - 94 m tablets went to US, market price per tablet is ~\$ 6.14
 - 33 m tablets to RoW primarily EU, price per tablet is ~ \$ 1.89. Italy ~ € 1
- **Shire Phase III diverticulitis data is expected mid 2012**
 - Could provide an additional peak sales of ~\$ 500m

Budesonide MMX: Evaluation of Efficacy

- **UCDAI: composite score system including individual assessments (scored 0-3) of**
 - Stool Frequency
 - Rectal Bleeding
 - Endoscopy (Colonoscopy)
 - Physician's Rating of Disease Activity
- **Primary Endpoint: the most severe criteria have been applied**
 - **Remission** at Week 8 defined as UCDAI score ≤ 1 with:
 - Rectal bleeding score = 0 AND
 - Stool frequency score = 0 AND
 - Normal mucosa (no friability) on colonoscopy *AND*
 - Endoscopic Index Score with ≥ 1 point reduction from baseline

Budesonide MMX efficacy vs Placebo and Entocort in EU phase III trial

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%)	

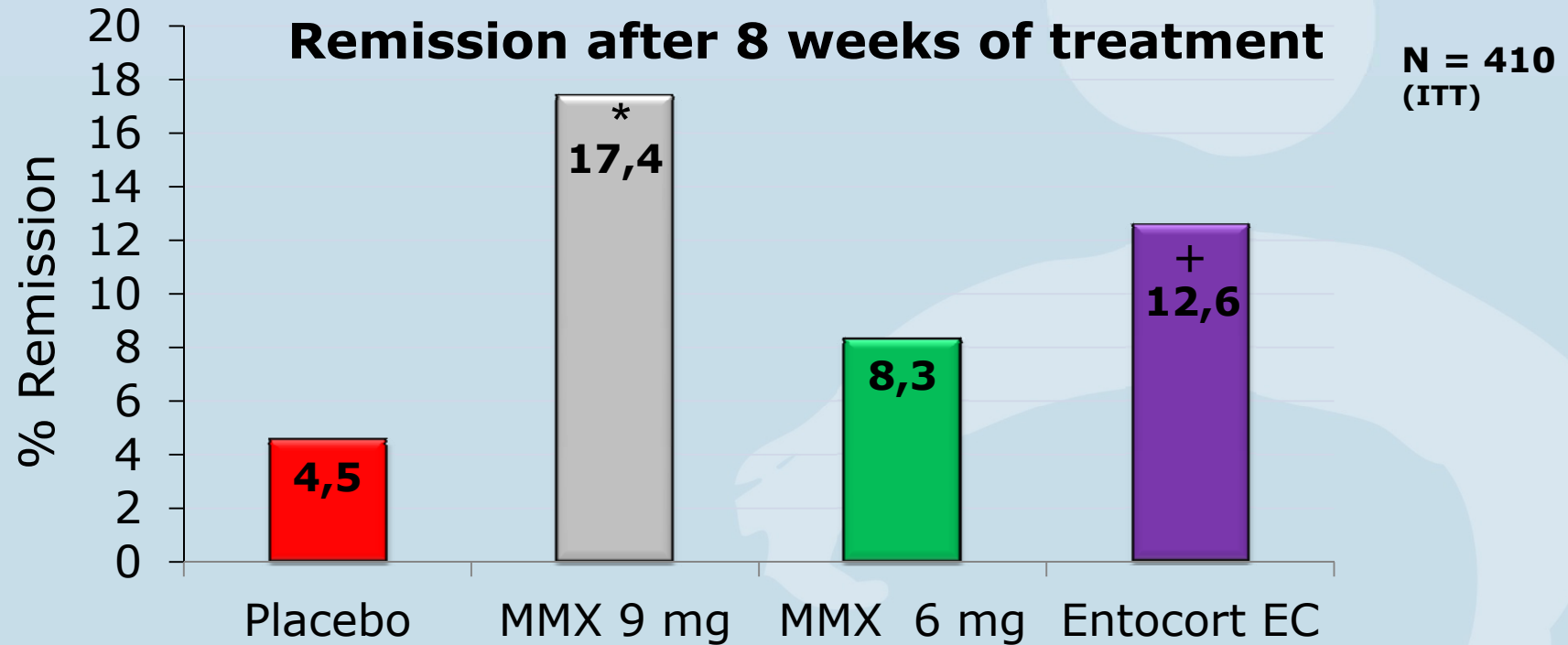
*Statistically significant vs placebo at 0.025

** Statistically significant vs placebo at 0.05

^(a)Not powered to show statistical difference between MMX arms and Entocort

Budesonide MMX EU Phase 3 Study Results

Primary Efficacy Endpoint



	N=89	N=109	N=109	N=103
Remission, n(%)	4 (4.5)	19 (17.4)	9 (8.3)	13 (12.6)
Δ vs. Placebo	--	12.9%	3.8%	8.1%
P-value	--	0.0047*	0.2876	0.0481+

* Statistically significant ($p < 0.025$)

+ Statistically significant ($p < 0.05$)

Study not powered to show a statistical difference between budesonide MMX[®] and Entocort[®] EC treatment arms

Budesonide MMX US Phase III study

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 2400 mg	124	15 (12.1%)	0.22 ^(a)
Placebo	121	9 (7.4%)	

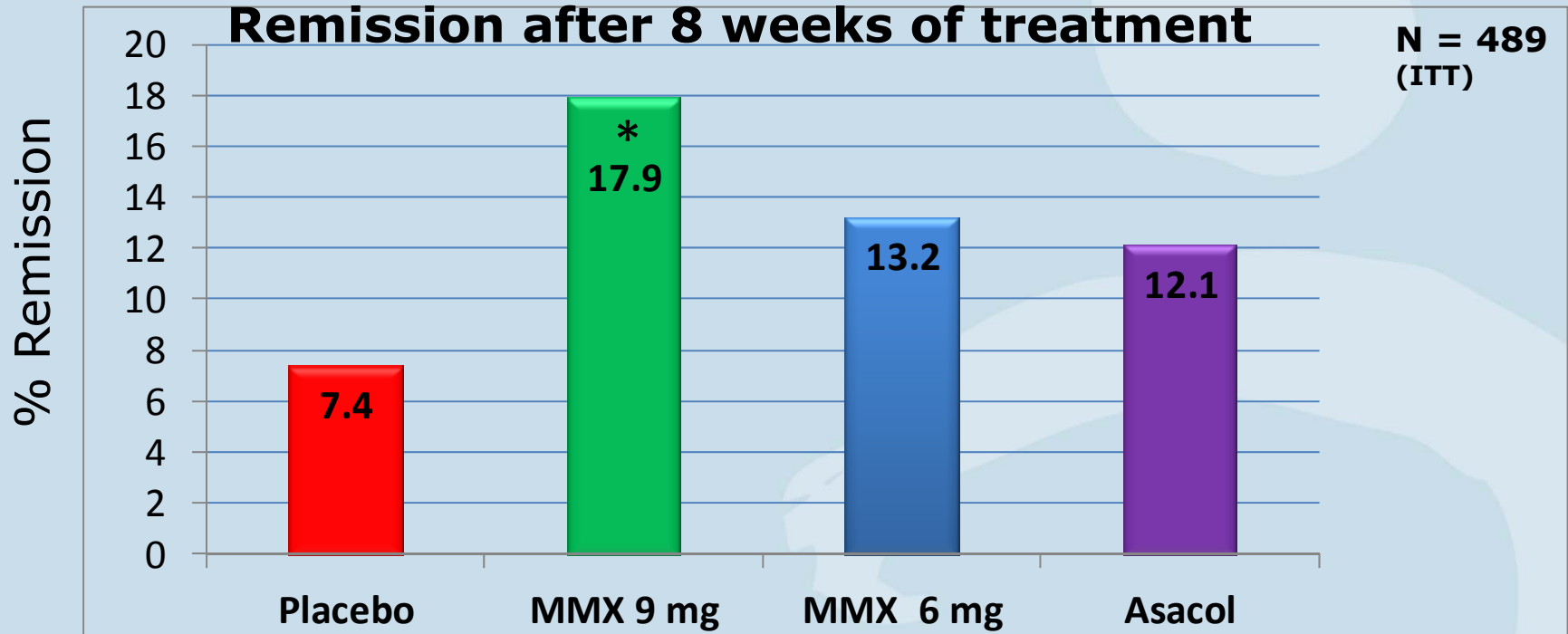
Treatment arm	Number of patients PP	Patients in remission	P-value
Budesonide MMX 9 mg	69	20 (29.0%)	0.0027*
Budesonide MMX 6 mg	72	11 (15.3%)	0.2110
Asacol 2400 mg	73	10 (13.7%)	0.3144 ^(a)
Placebo	61	9 (8.2%)	

*Statistically significant vs placebo

^(a)Not powered to show statistical difference

Budesonide MMX US Phase 3 Study Results

Primary Efficacy Endpoint



	N=121	N=123	N=121	N=124
Remission, n(%)	9 (7.4)	22 (17.9)	16 (13.2)	15 (12.1)
Δ vs. Placebo	--	10.4%	5.8%	4.7%
P-value	--	0.0143*	0.1393	0.2200

* Statistically significant (p < 0.025)

Not powered to show statistical difference between budesonide MMX® treatment arms and Asacol®

Budesonide MMX vs comparators (Entocort® and Asacol®)

Budesonide MMX vs:	Response Ratio (remission)
Entocort® (EU)	~140%
Asacol® (US)	~148%

Budesonide MMX: Clinical relevance

- **Remission rates of different trials cannot be compared**
 - populations vary
 - clinical practices vary
 - primary end points vary
 - assessment tools vary
- **Only way to compare different clinical trials is using Odds Ratio**
 - compares drug to placebo ratio
 - Budesonide MMX has a superior Odds Ratio to golden standard Lialda®

	Odds Ratio
Lialda® 2.4 g/die	2.40
Lialda® 4.8 g/die	2.47
Budesonide MMX (EU)	4.49
Budesonide MMX (USA)	2.71

Budesonide MMX is a steroid: safety study crucial

Summary of Adverse Events in the Primary Analysis Group (Safety population, EU+US pooled data)

	Placebo [n=258, n(%)]	Bud-MMX 9mg [n=255, n(%)]	Bud-MMX 6mg [n=254, n(%)]
Patients with any AE	138 (53.5%)	144 (56.5%)	154 (60.6%)
Related	65 (25.2%)	69 (27.1%)	63 (24.8%)
Not Related	73 (28.3%)	75 (29.4%)	91 (35.8%)
Mild	49 (19.0%)	57 (22.4%)	69 (27.2%)
Moderate	66 (25.6%)	67 (26.3%)	67 (26.4%)
Severe	21 (8.1%)	20 (7.8%)	17 (6.7%)
Leading to discontinuation	43 (16.7%)	39 (15.3%)	48 (18.9%)
Patients with any SAE	8 (3.1%)	7 (2.7%)	5 (2.0%)

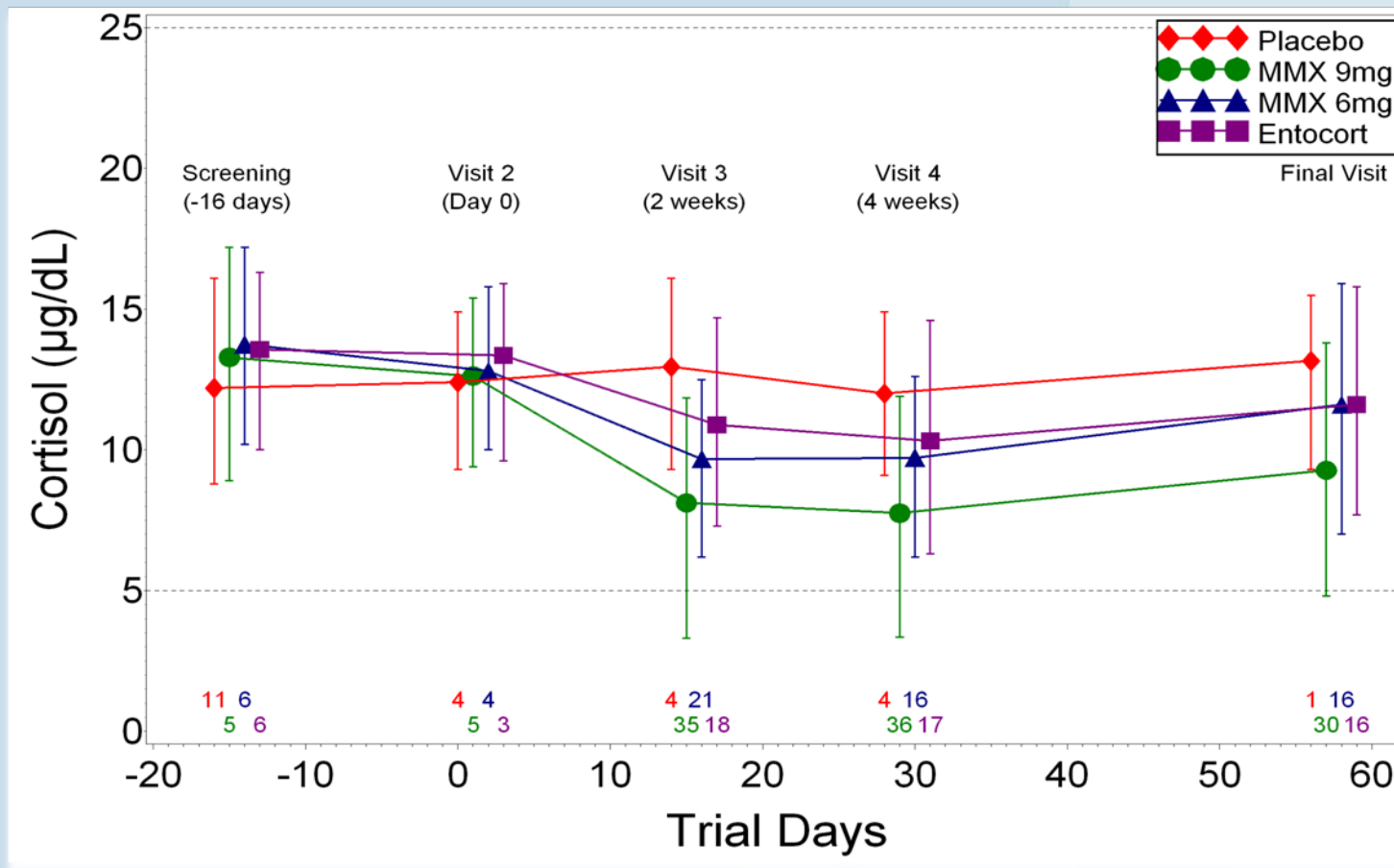
Safety of Budesonide MMX: Signs and Symptoms of Glucocorticoid Effects

Number of patients with worsening from baseline

Effect	Placebo N=129 N (%)	BUD-MMX 9 mg N=128 N (%)	BUD-MMX 6 mg N=128 N (%)	Entocort® N=126 N (%)
Overall	11 (8.5)	7 (5.5)	7 (5.5)	12 (9.5)
Moon Face	4 (3.1)	2 (1.6)	0 (0.0)	1 (0.8)
Striae Rubrae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flushing	1 (0.8)	0 (0.0)	1 (0.8)	1 (0.8)
Fluid Retention	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Mood Change	7 (5.4)	2 (1.6)	3 (2.4)	6 (4.8)
Sleep Changes	4 (3.1)	3 (2.3)	3 (2.4)	7 (5.6)
Insomnia	2 (1.6)	1 (0.8)	2 (1.6)	3 (2.4)
Acne	2 (1.6)	1 (0.8)	1 (0.8)	3 (2.4)
Hirsutism	0 (0.0)	0 (0.0)	1 (0.8)	2 (1.6)

No evidence of increase in glucocorticoid effects observed in Budesonide MMX vs. placebo

Safety of Budesonide MMX: Effect of Budesonide MMX on Morning Plasma Cortisol



Symbols indicate mean plasma cortisol level for each visit for each treatment
 Numbers at the bottom of the graph are the number of patients at each visit that had plasma cortisol levels below the lower limit of normal (5 µg/dL).

Extension trial results: safety is confirmed

- **Aim:**

- evaluate the long-term safety and tolerability of Budesonide MMX 6 mg
- administered to patients in remission
- measuring the delay in relapsing time

- **Trial design**

- double blind, multicenter 12-month extended use study in patients treated daily with Budesonide MMX 6 mg or placebo
- Patients enrolled: 123 from EU, USA, Canada, India

- **Safety results**

- Frequency of **treatment related adverse events** for Budesonide MMX 6 mg (21.0%) was similar to placebo (21.3%).
- **Mean morning plasma Cortisol levels** remained within normal limits at all visits for both Budesonide MMX 6 mg and placebo.
- No clinically meaningful differences in number of patients with **abnormal bone mineral density scans** at baseline and end-of-study between Budesonide MMX 6 mg and placebo.

Extension trial results: outlook of efficacy

Even though the extended use study wasn't powered to show statistical significance, it also explored the efficacy of Budesonide MMX 6 mg in maintenance of remission of ulcerative colitis compared to placebo

- Statistically significant difference between Budesonide MMX 6mg from placebo for the primary endpoint (percentage of patients achieving clinical remission at 1, 3, 6, 9 and 12 months) wasn't achieved
- A higher percentage of placebo patients (59.4%) experienced clinical relapse vs. the Budesonide MMX 6 mg group (30.8%)
- The median time to clinical relapse (number of days without a new flare) was longer for Budesonide MMX 6 mg treatment group compared to placebo group

Budesonide MMX: the approval process in EU

- **Filed MAA with Dutch Regulatory Authority following the DCP procedures in Q2 2011, expected approval in Q2 2012**
- **Registrations are all made in name of Cosmo**
- **Marketing partner is Ferring worldwide except USA and Japan**
- **1st stage DCP registration:**
 - Netherlands (RMS), Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Portugal, Hungary, Spain, Sweden and UK
- **2nd stage MRP registration:**
 - Bulgaria, Cyprus, Czech Republic, Estonia, Iceland, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Romania, Slovak Republic, Slovenia
- **RoW priority markets of Ferring:**
 - Canada, Brazil, Mexico, Australia, New Zealand, Middle East, Turkey

Budesonide MMX EU launch project and expectations

- **Brand name in EU**
 - Cortiment MMX®
- **Target population**
 - around 0.5 m persons
 - 75% of patients are mild to moderate
 - Of these 30% are in acute phase and 70% in remission
- **Product positioning**
 - Clinical trials results assure that in our tested patient population Budesonide MMX resulted more efficient than Entocort® and safer than systemic steroids
 - Competing product price of Entocort®: ~ \$ 7.65 per 3x3 mg tablet

Budesonide MMX USA approval process

- **Submission to FDA on December 19, 2011**
- **Acceptance for filing within 60 days after submission to FDA**
- **NDA reviewed by FDA in ~10 months from date of submission**
- **PDUFA date likely to be in October 2012**
- **Licensee for USA is Santarus**

Budesonide MMX launch process and expectations

- **Brand name**
 - Uceris®
- **Target population in US**
 - around 730'000 persons
- **Launch likely Q1 2013**
 - Compete against systemic steroids, azathioprine and to some extent 5 ASAs
 - Possible use in combination with 5 ASAs
 - Pricing undecided but likely guided by Entocort EC (approved for CD)
 - Entocort EC price in USA ~ \$ 54 per 3x3 mg tablet
- **Peak sales projected at \$ 300 m by Santarus**

Rifamycin SV - MMX

- **Indication**

- Travellers and Infectious Diarrhoea

- **Status**

- **Positioned as New Chemical Entity in USA, as known drug in Europe**
- **Phase III EU trial (by Dr. Falk Pharma)**
 - Randomized, double-blind, double-dummy, multi-centre, comparative parallel-group study to evaluate the efficacy and safety of oral daily Rifamycin SV-MMX 400 mg b.i.d. vs. Ciprofloxacin 500 mg b.i.d. in the treatment of acute infectious diarrhoea in travellers
 - **Status:** recruitment to interim analysis point completed. Analysis expected Q1 2012
- **Phase III US trial (by Santarus)**
 - Randomized, double-blind, multi-centre, placebo-controlled study to evaluate the efficacy and safety of Rifamycin SV MMX for the treatment of travellers' diarrhea
 - **Status:** 60 further patients to be enrolled in order to complete recruitment of the first trial.

Rifamycin SV – MMX: New opportunities

- **New indications**

- Phase II P.O.C. for Diverticulitis in EU to be started in Q1 12 by Dr. Falk Pharma
- Second indication for USA for other intestinal diseases still in evaluation



- **Opportunities**

- Sister molecule of Rifaximin (Xifaxan/Salix; 2010 revenues \$ 340 m) with a broad range of possible application (H.E., CDI, IBS...)
 - Potentially very effective against Hepatic Encephalopathy and Clostridium Difficile
- More than 60% of people over the age of 60 have diverticulae
 - In 10-20% of cases the diverticula get infected and inflamed
 - No drug is currently approved for this disease

Cancer Statistics, 2012

Rebecca Siegel, MPH¹; Deepa Naishadham, MA, MS²; Ahmedin Jemal, DVM, PhD³

Estimated New Cases*

			Males	Females			
Prostate	241,740	29%			Breast	226,870	29%
Lung & bronchus	116,470	14%			Lung & bronchus	109,690	14%
<u>Colon & rectum</u>	<u>73,420</u>	<u>9%</u>			<u>Colon & rectum</u>	<u>70,040</u>	<u>9%</u>
Urinary bladder	55,600	7%			Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%			Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%			Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%			Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%			Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%			Ovary	22,280	3%
Pancreas	22,090	3%			Pancreas	21,830	3%
All Sites	848,170	100%	All Sites	790,740	100%		

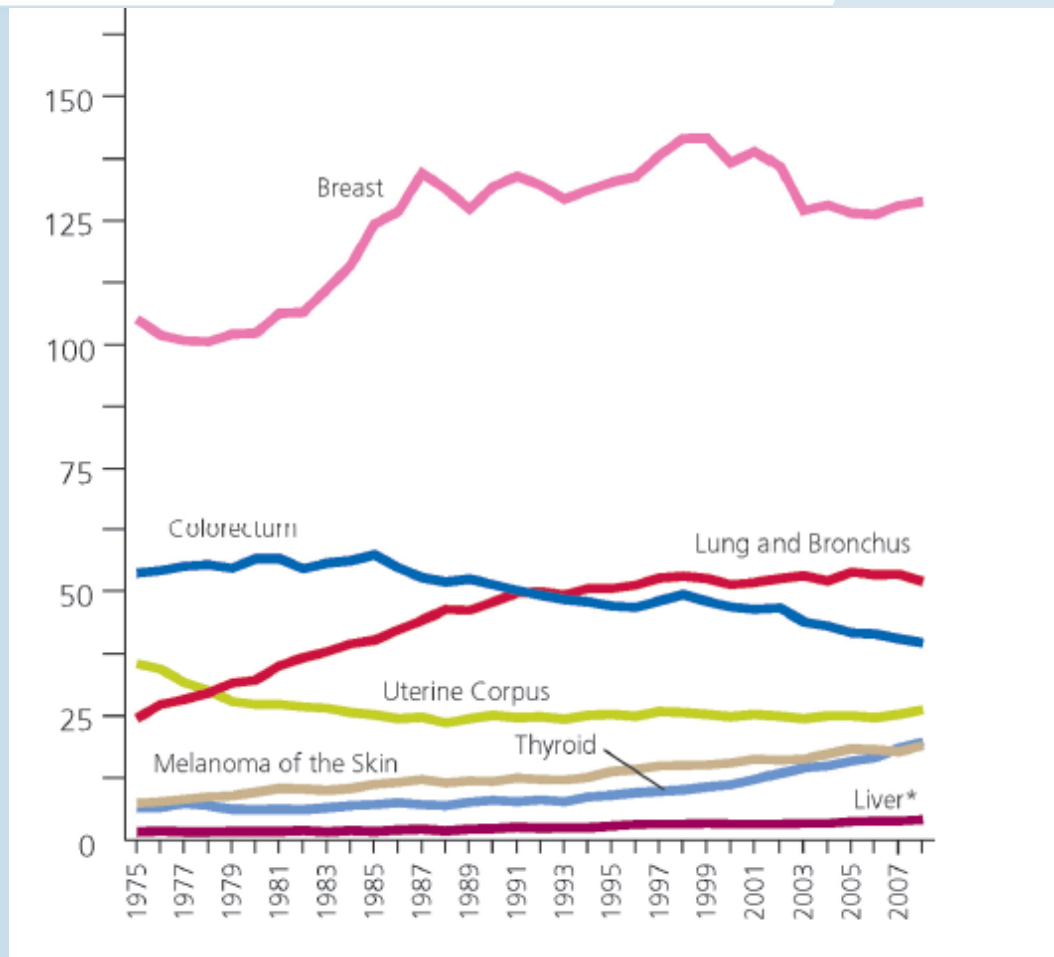
Colorectal cancer is the third leading cause of deaths for cancer in the Western Countries with at least **350,000** new cases expected in 2012 in USA+Europe

Very high death rate of colon cancer

TABLE 3. Death Rates for All Cancers Combined, 2004
United States, 2012

STATE	DEATH RATE†	ALL SITES	BRAIN & OTHER NERVOUS SYSTEM	FEMALE BREAST	COLON & RECTUM
Alabama	199.9	10,290	230	710	980
Alaska	181.2	930	‡	70	80
Arizona	156.2	11,090	300	780	1,010
Arkansas	201.7	6,570	150	420	610
California	165.1	56,620	1,540	4,110	5,140
Colorado	156.1	7,190	230	510	680
Connecticut	176.9	6,940	160	480	560
Delaware	196.6	1,930	50	120	170
Dist. of Columbia	198.3	1,010	‡	80	100
Florida	172.5	42,170	850	2,600	3,660

Colon cancer death rate is coming down



Based on the most recent data, the overall colon cancer death rate decreased by 0.8% per year in male and 0.9% in female

Screening program for colorectal cancer has reduced death rate

- **All western countries have adopted mass screening program in asymptomatic patients**
- **Male and female between 50 and 65 are targeted to screening program**
- **Colonoscopy is the most frequently adopted and most effective method for colon evaluation**
- **Hundreds of millions of people are expected to undergo screening colonoscopy in the next ten years**

Screening programs for colorectal cancer

National Cancer Institute
at the National Institutes of Health

Questions About Cancer?
1-800-4-CANCER

SEARCH

NCI Home

Cancer Topics

Clinical Trials

Cancer Statistics

Research & Funding

News

About NCI

NATIONAL CANCER INSTITUTE
FactSheet

In English | En español



Reviewed: 12/30/2011

Search Fact Sheets by Keyword

GO

View Fact Sheets by Topic

[Cancer Type](#)

[Risk Factors and Possible Causes](#)

[Prevention](#)

[Detection/Diagnosis](#)

[Cancer Therapy](#)

[Support/Coping/Resources](#)

[Tobacco/Smoking Cessation](#)

[Information Sources](#)

Colorectal Cancer Screening

Key Points

- Colorectal cancer is a disease in which cells in the colon or rectum become abnormal and divide without control, forming a mass called a tumor.
- The exact causes of colorectal cancer are not known. However, studies show that certain factors increase a person's chance of developing colorectal cancer.
- Health care providers may suggest one or more tests for colorectal cancer screening, including a fecal occult blood test (FOBT); sigmoidoscopy; regular, or standard, colonoscopy; virtual colonoscopy; or double contrast barium enema (DCBE).
- People should talk with their health care provider about when to begin screening for colorectal cancer, what tests to have, the benefits and risks (potential harms) of each test, and how often to schedule appointments.
- New methods, such as the genetic testing of stool samples, to screen for colorectal cancer are under study.



NHS Bowel Cancer Screening Programme

NHS

Cancer Screening Programmes

NHS Cancer Screening Programmes

Contact Us

Press Room

Literature Database

Search

NHS Breast Screening Programme

NHS Cervical Screening Programme

NHS Bowel Cancer Screening Programme

NHS Prostate Cancer Risk Management

Welcome to the NHS bowel cancer screening website for England

Questions about Bowel Cancer Screening? Call the HELPLINE
0800 707 60 60

You can ring this number to request a screening kit if you are over 70



The NHS Bowel Cancer Screening Programme is now fully rolled out.

This means that most people in their sixties will have already received an invitation from the programme.

[NHS BCSP home page](#)

[Programme publications](#) →

[About bowel screening](#) →

[More information about the](#)

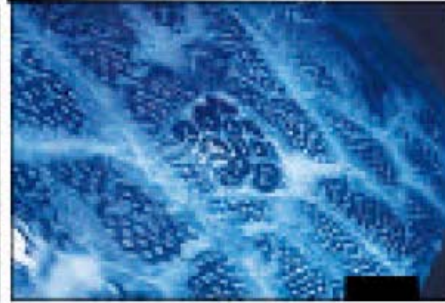
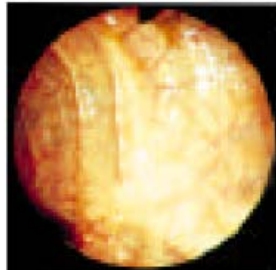
Why a screening program for colorectal cancer?

Colorectal cancer comes through a precursor: the polyp

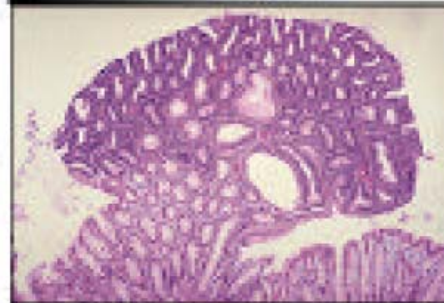
Normal mucosa



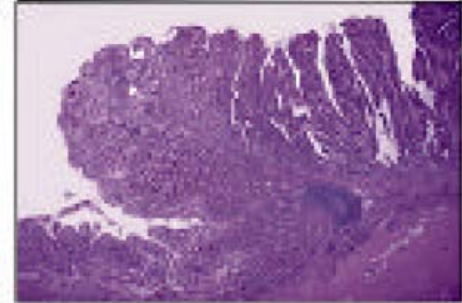
tiny polyp



large polyp

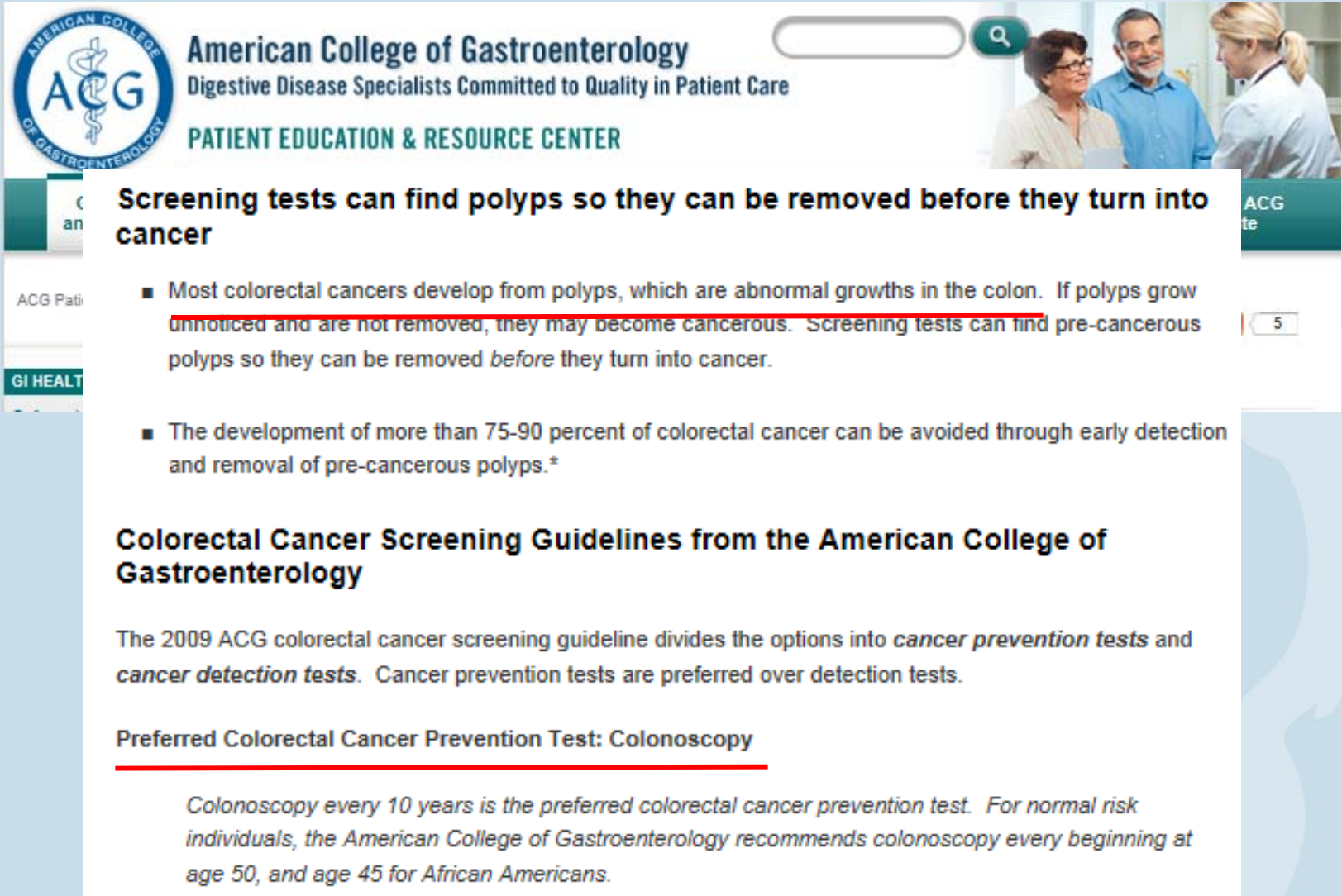


malignant tumor



The adenoma-carcinoma sequence

75-90% of colorectal cancer can be avoided by early detection



American College of Gastroenterology
Digestive Disease Specialists Committed to Quality in Patient Care
PATIENT EDUCATION & RESOURCE CENTER

Screening tests can find polyps so they can be removed before they turn into cancer

- Most colorectal cancers develop from polyps, which are abnormal growths in the colon. If polyps grow unnoticed and are not removed, they may become cancerous. Screening tests can find pre-cancerous polyps so they can be removed *before* they turn into cancer.
- The development of more than 75-90 percent of colorectal cancer can be avoided through early detection and removal of pre-cancerous polyps.*

Colorectal Cancer Screening Guidelines from the American College of Gastroenterology

The 2009 ACG colorectal cancer screening guideline divides the options into *cancer prevention tests* and *cancer detection tests*. Cancer prevention tests are preferred over detection tests.

Preferred Colorectal Cancer Prevention Test: Colonoscopy

Colonoscopy every 10 years is the preferred colorectal cancer prevention test. For normal risk individuals, the American College of Gastroenterology recommends colonoscopy every beginning at age 50, and age 45 for African Americans.

The colonoscopy goal

- Explore the entire organ
- Identify all precursor lesions (polyps)
- Remove the polyp to interrupt the adenoma-carcinoma sequence



Colonoscopy performance

Polyp Miss Rate Determined by Tandem Colonoscopy: A Systematic Review

Jeroen C. van Rijn, M.D.,¹ Johannes B. Reitsma, M.D., Ph.D.,¹ Jaap Stoker, M.D., Ph.D.,²
Patrick M. Bossuyt, Ph.D.,¹ Sander J. van Deventer, M.D., Ph.D.,³ and Evelien Dekker, M.D., Ph.D.³
¹Departments of Clinical Epidemiology & Biostatistics; ²Radiology; and ³Gastroenterology, Academic Medical
Center (University of Amsterdam), Amsterdam, The Netherlands

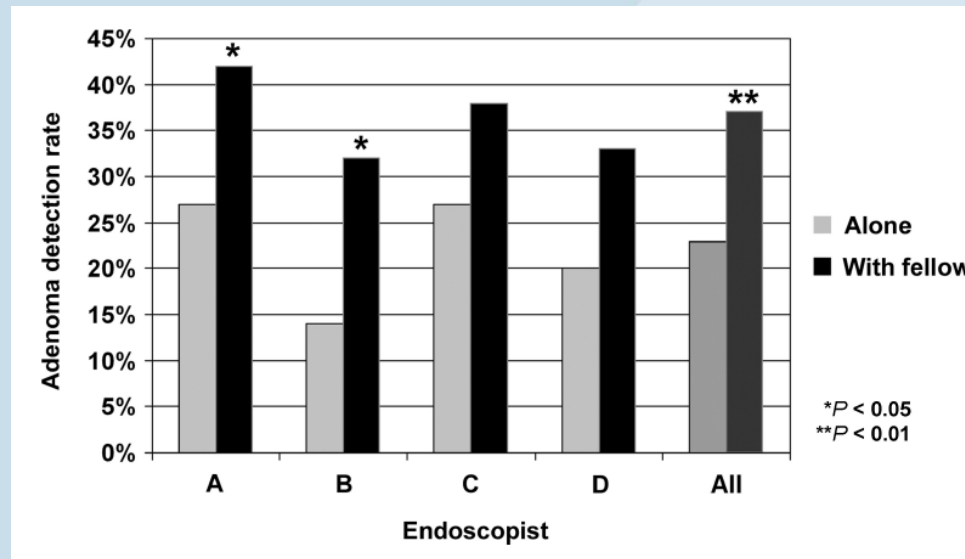
Colonoscopy is the best available method to detect and remove colonic polyps and therefore serves as the gold standard for less invasive tests such as virtual colonoscopy. Although gastroenterologists agree that colonoscopy is not infallible, there is no clarity on the numbers and rates of missed polyps. The purpose of this systematic review was to obtain summary estimates of the polyp miss rate as determined by tandem colonoscopy.

Six studies with a total of 465 patients could be included. The pooled miss rate for polyps of any size was 22% (95% CI: 19–26%; 370/1,650 polyps). Adenoma miss rate by size was, respectively, 2.1% (95% CI: 0.3–7.3%; 2/96 adenomas ≥ 10 mm), 13% (95% CI: 8.0–18%; 16/124 adenomas 5–10 mm), and 26% (95% CI: 27–35%; 151/587 adenomas 1–5 mm). Three studies reported data on

Colonoscopy misses about 1/3 of polyps below 10 mm thus leading to significant negative impact of cancer prevention

Polyp (adenoma) detection rate is extremely variable

- operator dependent (experts vs beginners or non-experts)
- hospital dependent (academic vs general hospital)



ORIGINAL ARTICLE

Quality Indicators for Colonoscopy and the Risk of Interval Cancer

person-years. The endoscopist's rate of detection of adenomas was significantly associated with the risk of interval colorectal cancer ($P=0.008$), whereas the rate of

CONCLUSIONS

The adenoma detection rate is an independent predictor of the risk of interval colorectal cancer after screening colonoscopy.

Devices to improve colon polyp detection

- Based on the current data, wide-angle colonoscopy and electronic chromoendoscopy do not appear to improve polyp or adenoma detection rate
- Results for cap-fitted colonoscopy related to polyp detection are mixed, but inconclusive
- The TER is a promising tool in assisting standard colonoscopy to improve visualization of colonic areas otherwise difficult to access but presently not adoptable in clinical practice
- Pancolonic or targeted methylene blu or indigo carmine staining, with or without magnification or high-resolution endoscopy, is the most widely used chromoendoscopic technique for the detection or differentiation of colon polyps and neoplasms
- Prospective and randomized trials have shown methylene blue chromoendoscopy to be of benefit in enhancing the detection of dysplasia in chronic ulcerative colitis (CUC)

What does chromoendoscopy mean?

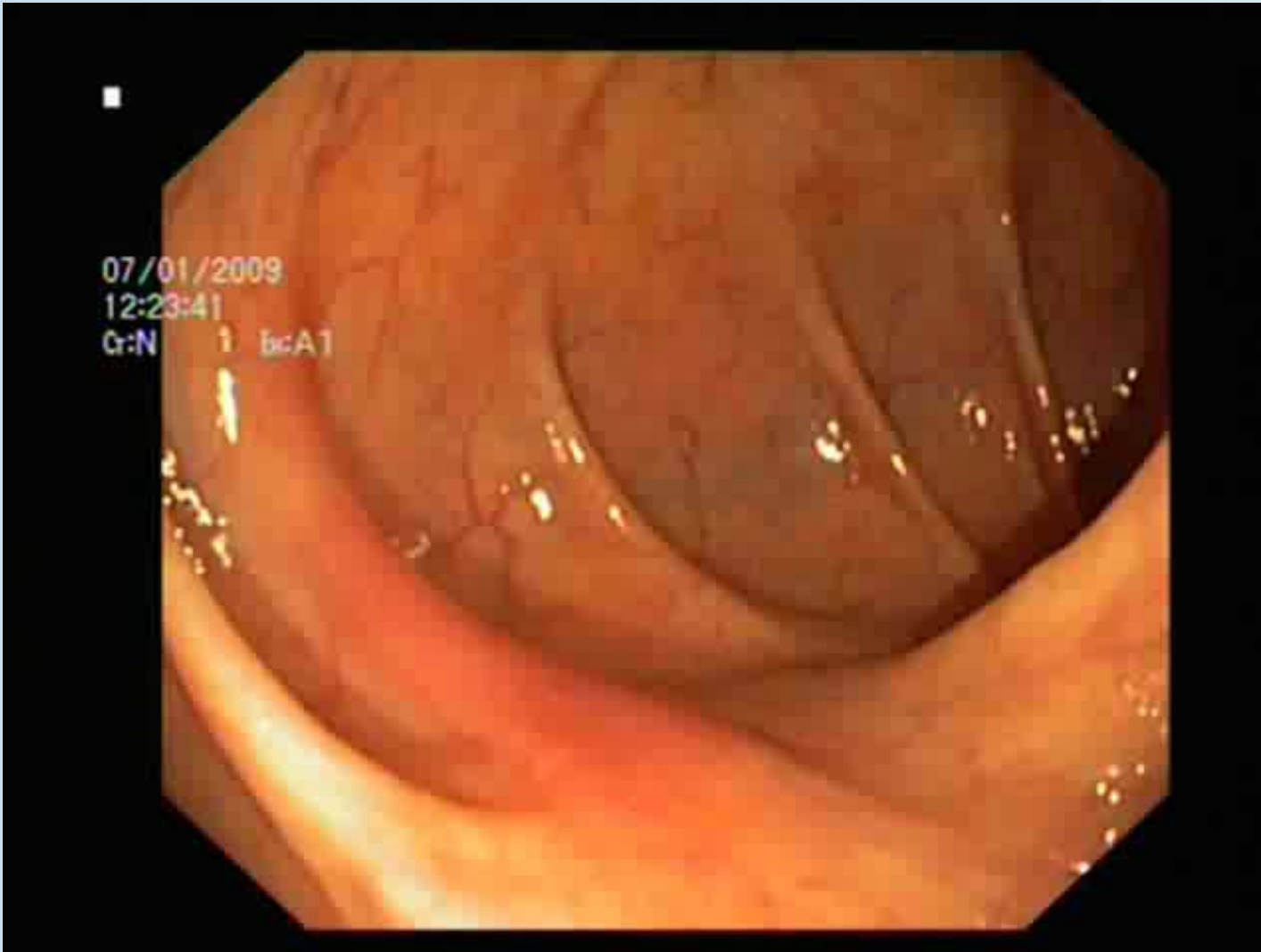


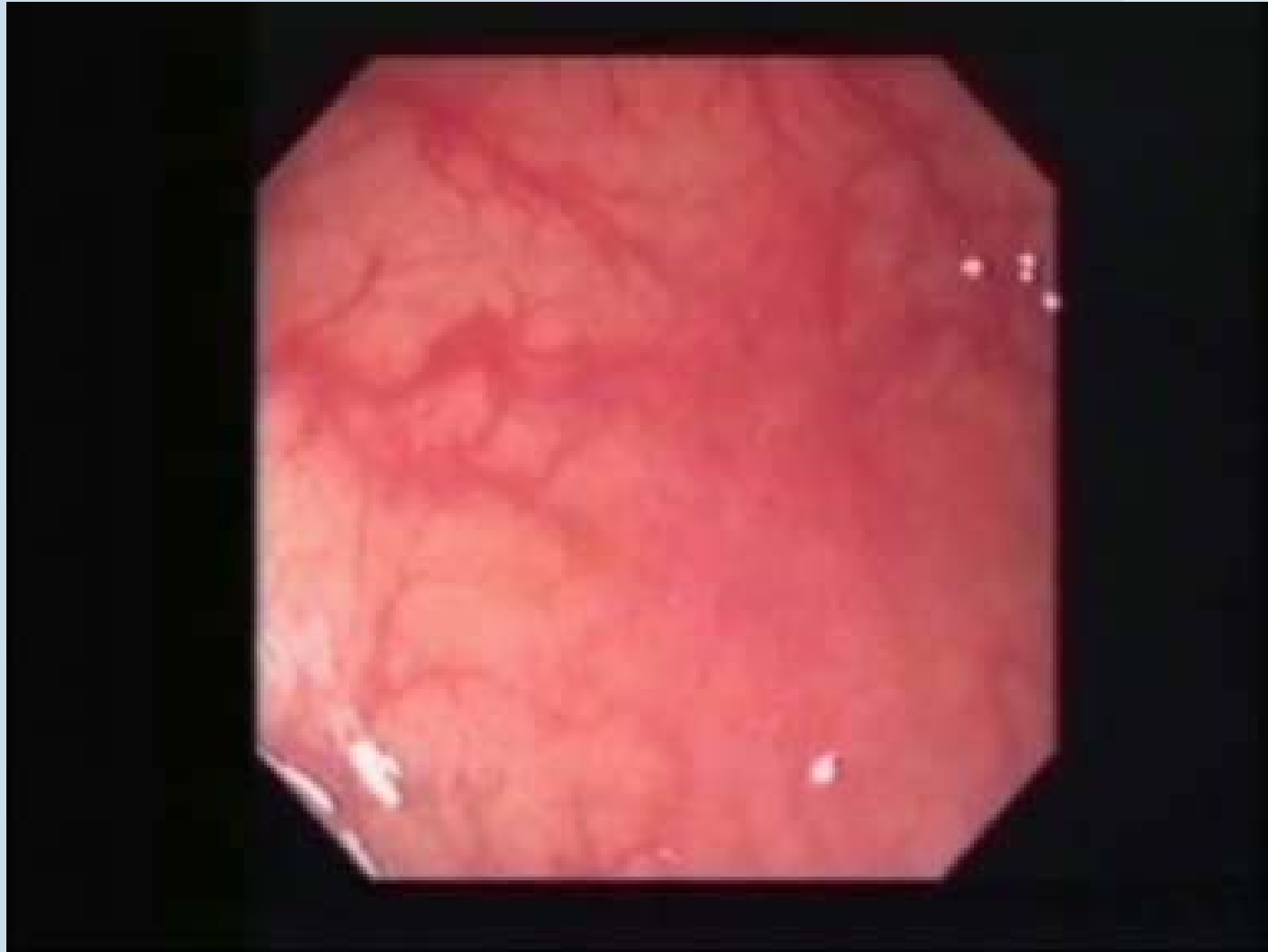
TECHNOLOGY STATUS EVALUATION REPORT



Chromoendoscopy

- **Chromoendoscopy, or chromoscopy, refers to the topical application of stains or dyes at the time of endoscopy in an effort to enhance tissue characterization, differentiation, or diagnosis**
- **A search of the MAUDE database did not identify any reported complications related to chromoendoscopy**
- **Should be used on a routine basis to improve polyp detection rate in patients undergoing colonoscopy**





Chromoendoscopy is not routinely used in daily practice

- In spite of international guide-lines and recommendations from the most important scientific societies **chromoendoscopy has not been able to become the standard practice**
 - It's time consuming
 - Dirty technique
 - Challenging for nurses and doctors
 - Requires staining preparation and spraying during the procedure

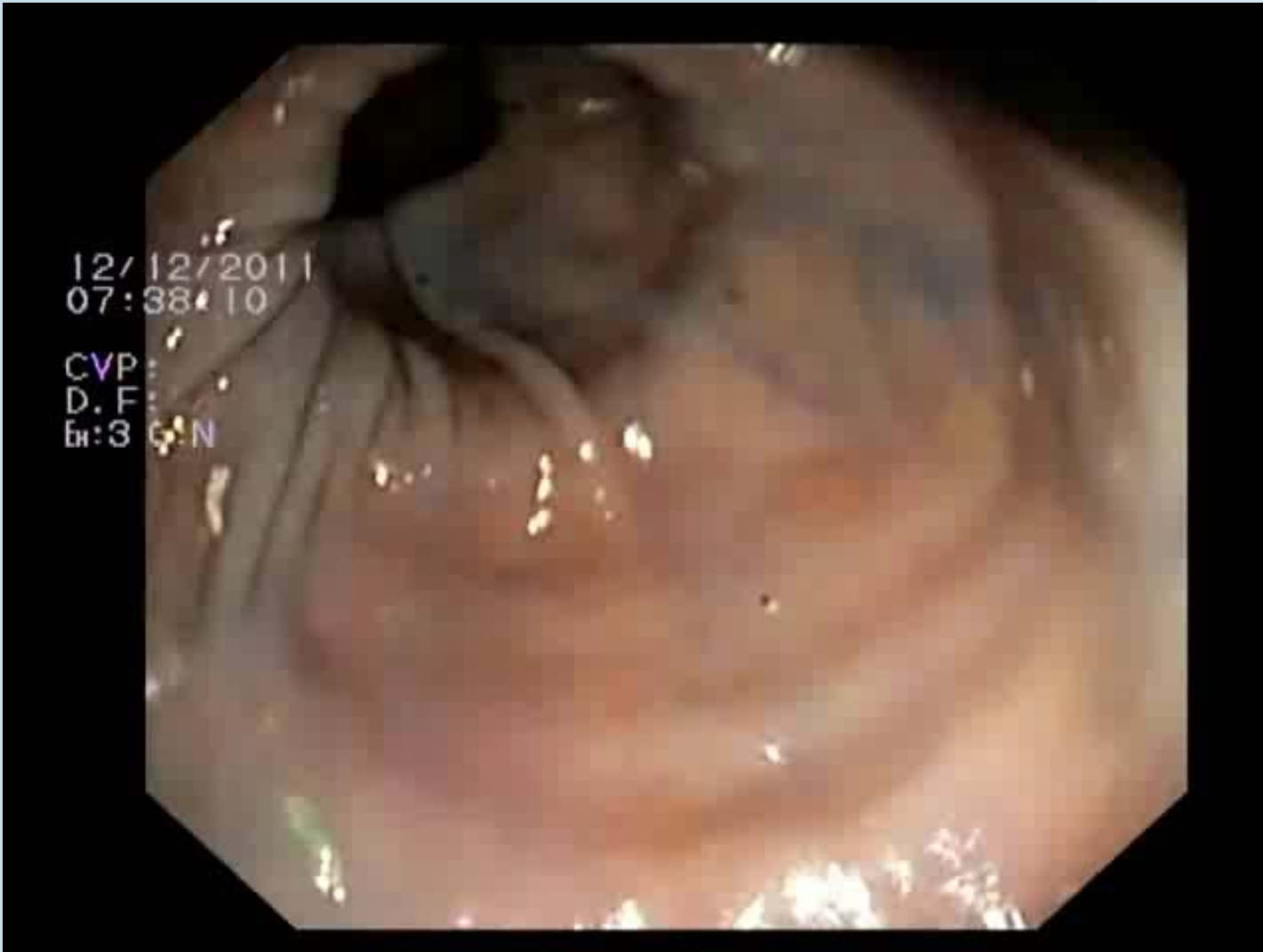
The requirements to overcome the problem

- **Provide the staining substance during standard bowel preparation**
- **Release the methylene blue through the entire length of colon**
- **Mucosa staining is homogenous and reliable**
- **No additional time is required pre- or during the endoscopic manouvers**

27/09/2011
09:54:50

CVP:
D.F:
Et:1 Gr:N





Methylene Blue MMX, the transformational business case

- **Indication**
 - Colon cancer and IBD dysplasia diagnostic
- **Rationale**
 - Requires identical skills to those developing Lialda®
- **Advantages for patient**
 - Decreases subjectivity of gastroenterologist
 - Increases yield on identifying polyps and mucosal lesions substantially
 - Will dramatically increase proportion of colon cancer patients that are detected early
- **Market size**
 - ~25 million colonoscopies projected for 2012 in USA and EU. With improved detection rate incentive for colonoscopies should rise
- **Competition**
 - local non approved liquid applications sprayed via endoscope

Methylene Blue MMX, the regulatory strategy

- **Set up advisory board Q1 2012**
 - For cancer screening
 - For IBD screening
- **Determine requirements of Regulatory Agencies**
- **Define target population**
- **Design clinical endpoints**
 - Diagnostic efficiency
 - Safety confirmation

Methylene Blue MMX

Global Advisory Board 10–11 March 2012

- **Objective**

- Capture world wide renown scientific, applicatory and regulatory experience
- Global KOLs will be attending

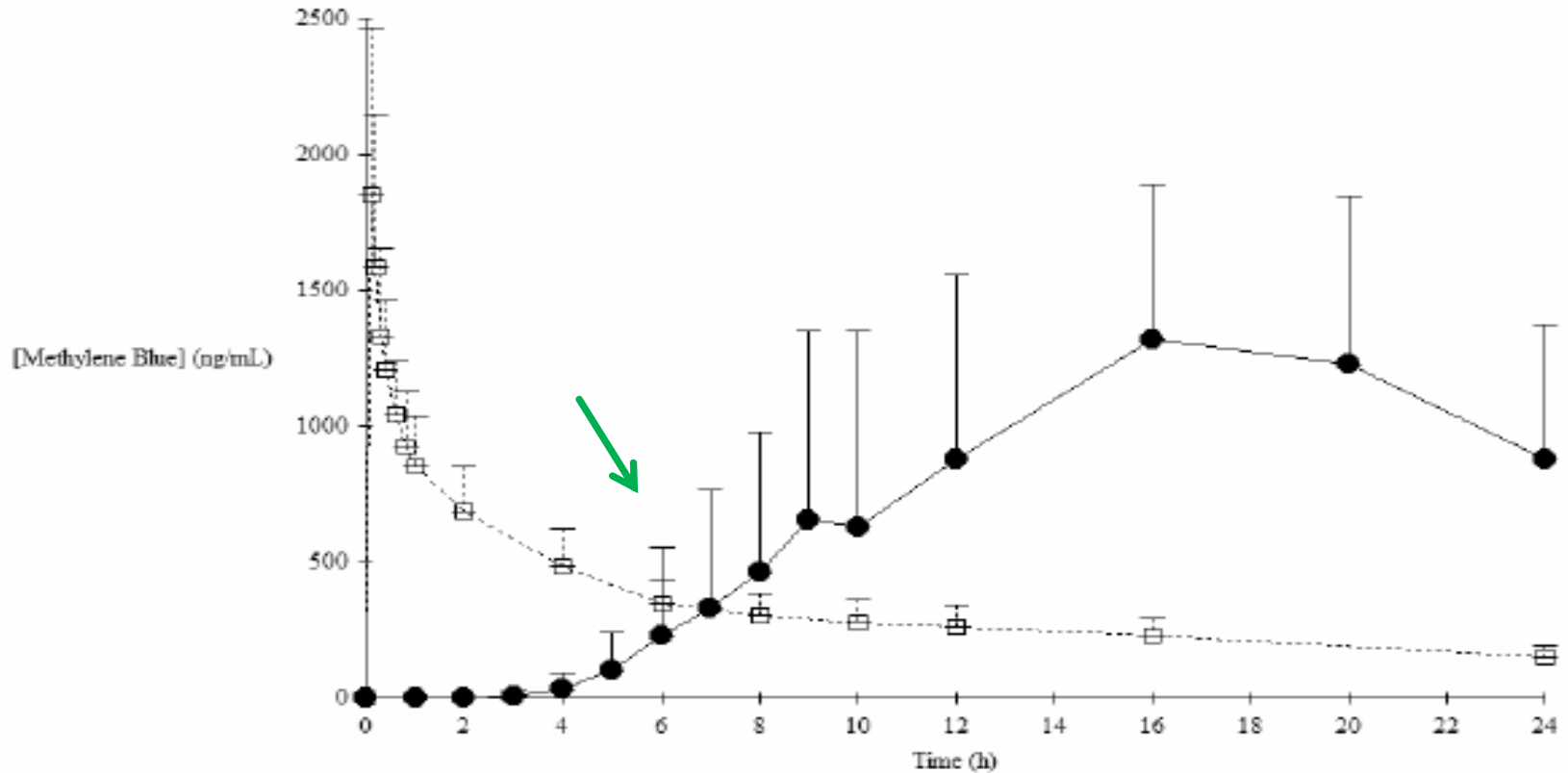
- **Cancer screening group**

- James EAST, *John Radcliffe Hospital, Oxford, UK*
- Ralph KIESSLICH, *Johannes Guttenberg University, Mainz, Germany*
- Alessandro REPICI, *Humanitas Hospital, Milan, Italy*
- Michael WALLACE, *Mayo Clinic, Jacksonville (FLA), USA*

- **IBD Group**

- Silvio DANESE, *Humanitas Hospital, Milan, Italy*
- Geert D'HAENS, *Academic Medical Center, Amsterdam, NL*
- Sunanda KANE, *Mayo Clinic, Rochester (MIN), USA*
- Willian SANDBORN, *UC Medical Center, San Diego (CA), USA*
- Simon TRAVIS, *John Radcliffe Hospital, Oxford, UK*

Methylene Blue MMX PK study



Mean (+SD) blood Methylene Blue concentration (ng/mL) vs. time profiles after administration of one Methylene Blue MMX® 200 mg modified release tablet (● full line) and Methylene Blue 1% vials 10 mL (□ dotted line). Scale up to 24 h

Methylene Blue MMX clinical trial to optimize dosing and administration procedure

- **Study CB-17-01/03**
 - **Phase II dose ranging study to optimize staining procedure:**
 - >100 patients enrolled
 - Two doses tested: a single dose of 200 mg in divided doses of 25 mg resulted the optimal dose
 - Study completed
 - **Administration procedure optimized**
 - **Consistent colonic staining recorded**

Methylene Blue MMX ongoing clinical development (1/2)

- **Study CB-17-01/04**

Intraepithelial neoplasia detection rate after single oral dose of Methylene Blue MMX modified release tablets administered to patients with long standing ulcerative colitis undergoing colonoscopy

Open label, efficacy exploratory descriptive study

- **Test formulation: Methylene blue MMX 25 mg** modified release tablets
- **Investigator: Silvio Danese, MD**, *Centre for Research and Care of Intestinal Diseases, Department of Gastroenterology IRCCS Istituto Clinico Humanitas, Rozzano University of Milan School of Medicine, Italy*
- **Endpoints:**
 - **Primary endpoint** to evaluate and describe the intraepithelial neoplasia detection rate after colonic mucosal staining obtained with single dose of 200 mg of methylene blue MMX tablets administered during and at the end of the intake of the bowel cleansing preparation
 - **Secondary endpoint** to evaluate the extent and severity of the inflamed mucosa.

Methylene Blue MMX ongoing clinical development (2/2)

- **Study CB-17-01/05**

Polyp detection rate after single oral dose of Methylene Blue MMX modified release tablets administered to subjects undergoing outpatient colonoscopy

Open label, efficacy exploratory descriptive study

- **Test formulation:** Methylene Blue MMX 25 mg modified release tablets
- **Investigator:** Alessandro Repici, MD, Digestive Endoscopy Unit, Department of Gastroenterology IRCCS Istituto Clinico Humanitas, Rozzano University of Milan School of Medicine, Italy
- **End points:**
 - **Primary end-point** to evaluate and describe the polyp detection rate and the adenoma detection rate after colonic mucosal staining obtained with single dose of 200 mg of Methylene Blue MMX tablets administered during and at the end of the intake of the bowel cleansing preparation
 - **Secondary end-point:** to classify polyps and adenomas detected after colonic mucosal staining obtained with a single dose of 200 mg of methylene blue MMX tablets administered during and at the end of the intake of the bowel cleansing preparation. To evaluate the serrated lesion detection rate

Methylene Blue MMX Cost considerations

- **Cost projections 2012**

- Phase II b and Phase III start
- Milestone

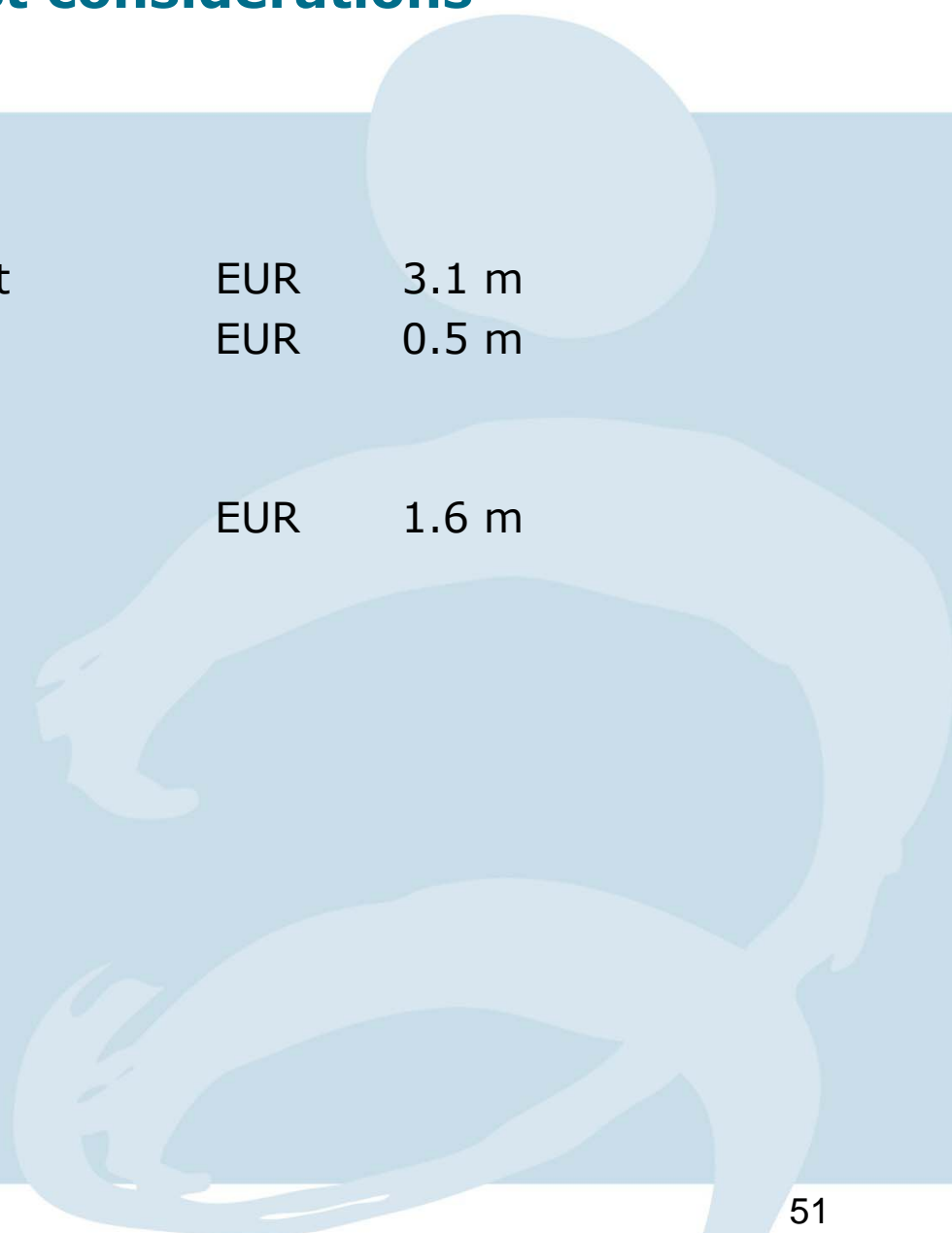
EUR 3.1 m

EUR 0.5 m

- **Cost Projections 2013**

- Complete Phase III

EUR 1.6 m



LMW Heparin MMX

- **The market for maintaining remission could be as large as the market for inducing remission**
 - Key physicians state that most important issue in IBD is to prolong remission until next relapse
 - Best UC inhibitors are biologics such as anti TNF α 's antibodies
 - None are approved, very expensive, may have serious side effects
 - LMW Heparin inhibits human intestinal epithelial cell inflammatory responses to TNF α , and other pro-inflammatory like IL 6 and IL 1b
 - It inhibits CD 4+T cells inducing Th1 and Th2 polarization
- **Decision to license out LMW Heparin MMX to potent US partner**
 - Parnaparin, the LMW Heparin candidate identified as most suitable, is not approved for use in USA where it is considered a NCE
 - New biologics have complex approval processes
 - Heparins have a tainted history in the US
- **An advisor has been mandated to find a partner**

CB-03-01: Cosmo New Chemical Entity (NCE)

- **Developing NCE is a high risk proposition**
 - **1 in 30 NCEs make it to the preclinic**
 - **1 in 3 of them pass to the Phase I**
 - **1 of 5 of them make it to the Phase III**
 - **And even then 10% fail to registrate**

What is the interest in the acne and alopecia market?

- **Very high unmet needs**

- 16% of US population suffer from acne
- 12% of all men have Alopecia
- 10% of all women have Hirsutism

- **Old concepts**

- Acne
 - 157 approved products, heavily genericized market
 - 60% of non generic WW revenue by drugs launched before 1996
 - Hormonal tablets frequently contraceptive linked
 - Topical applications are retinoids or anti-microbials
- Alopecia
 - Only one proprietary alopecia treatment, Propecia® \$ 440 m launched 1998
 - Vasodilators (Rogaine) off patent

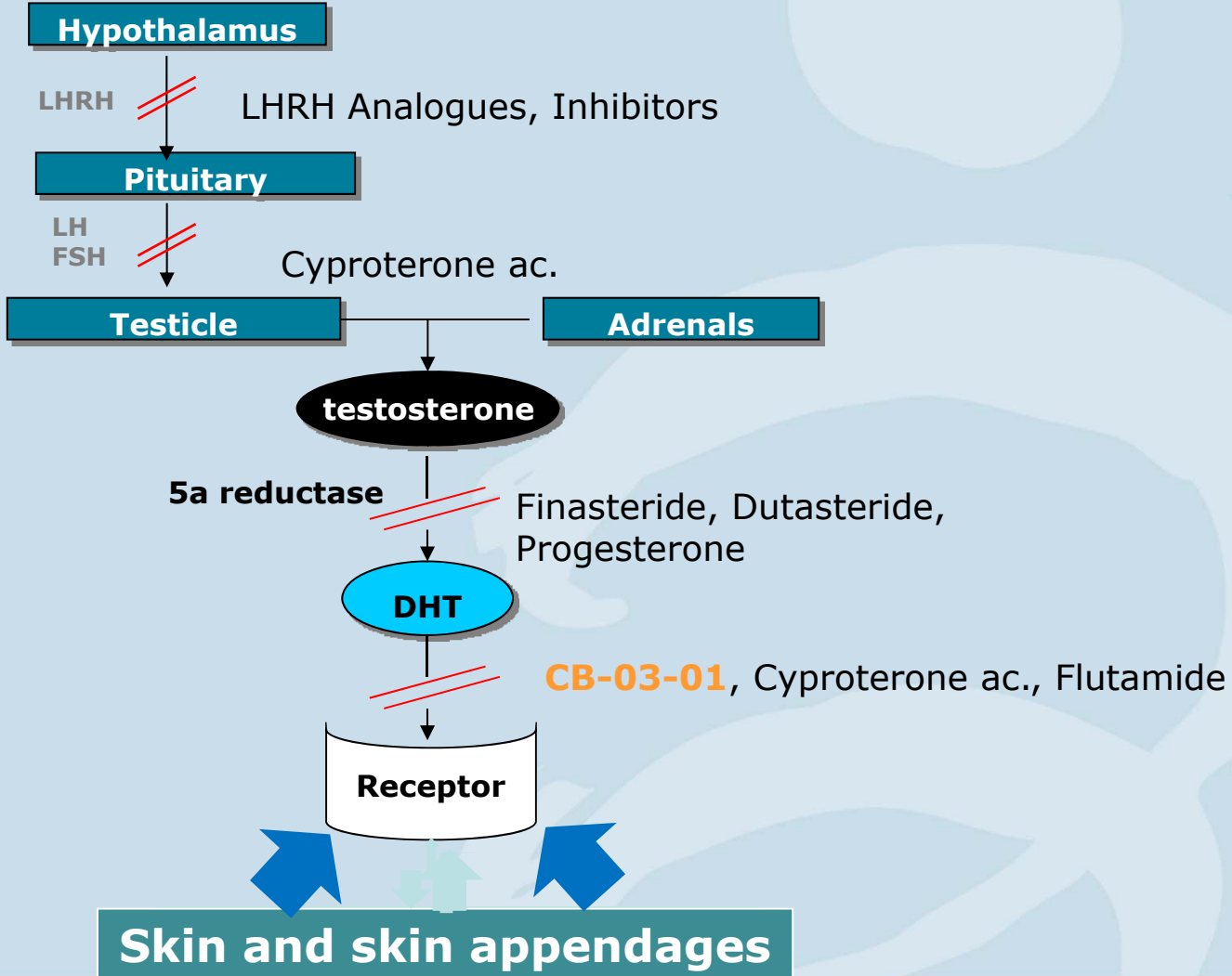
- **Thin pipeline**

- 2 anti acne agents in phase III, 12 in phase II
- Only two products in clinical development for alopecia

CB-03-01: Cosmo development path

- **Fulfil preclinical and basic clinical work**
 - Extensive preclinical evaluation program including pharmacology, toxicology and metabolism
 - CB-03-01 is safe and well tolerated
 - PoC trial in males
 - CB-03-01 is effective

Endocrine control of androgen production and mechanism of action of CB-03-01



The role of androgens in the development of acne

- **Antiandrogens are involved in the first step in a cascade of events that ultimately leads to the physical expression of acne**
 - Sebaceous gland cells (sebocytes) in the skin are androgen-sensitive and contain androgen receptors
 - Upon androgenic stimulation they increase production of sebum
 - The pilosebaceous follicle is obstructed by sebum excess
 - The obstruction and the continued androgen-stimulated excess sebum production dilates the follicle resulting in the formation of the acne lesion (comedo)
 - In presence of bacteria, infection and inflammation occur, the lesion worsens to papulas and pustulas
- **A topical acne product provided with an antiandrogenic activity as CB-03-01 can prevent the cascade of physiological events that leads to acne formation**

Pre-clinical evaluation of CB-03-01: important progress

<p>1.</p> <p>Complete pharmacological profile:</p>	<ul style="list-style-type: none">• Strong topical Antiandrogen• moderate anti-inflammatory• no other endocrine activities (progestinic, estrogenic)
<p>2.</p> <p>Complete toxicological profile:</p>	<ul style="list-style-type: none">• Acute, sub-acute, chronic toxicities in mouse, rat, rabbit, minipig. -> <i>very well tolerated to 150+ times human doses</i>• Reproductive toxicities in rat and rabbit -> <i>no effects on reproductive function.</i>• Skin and ocular irritation in rabbit -> <i>well tolerated by skin and eyes</i>• Safety pharmacology -> <i>no cardiac toxicity effects in dog.</i>• Mutagenesis (Ames test, chromosomal aberration test, micronucleus test in rat) -> <i>not mutagen.</i>
<p>3.</p> <p>Metabolism:</p>	<ul style="list-style-type: none">• Skin and Plasma of rat and human -> <i>simple and linear metabolism, quickly and completely metabolized to parent free cortexolone</i>• Hepatocytes from mouse, rat, rabbit, minipig, human -> <i>no main metabolic differences among animal species</i>• Human protein binding -> <i>more than 80% bound</i>• Not impacting on other drug metabolism

Summary Evaluation of CB-03-01

- **Pharmacology**

- Highly effective as topical antiandrogen without systemic effects
- Mild anti-inflammatory agent
- Acts as androgen-receptor blocker without interfering with metabolism of androgens

- **Safety**

- Not mutagen
- Well tolerated after repeated administration by subcutaneous and dermal route in rat, rabbit and minipig
- No safety concerns in materno-foetal development in rat and rabbit

- **Metabolism**

- Quickly and completely metabolized to inactive parent in skin and in plasma.
- No unexpected metabolites

- **FDA's REGULATORY FEEDBACK on Pre IND meeting:**

- Positive evaluation pre-clinical data provided
- Suggestions for the product clinical evaluation in the planned Ph. II dose range finding trial

CB-03-01 Clinical development history

• Clinical Development

- In Europe in 2008
- Phase 1 clinical trial CB-03-01 1% cream in healthy male volunteers evaluating local tolerability and pharmacokinetics
- Second Phase 1 study in healthy male and female volunteers in which the material was applied for 14 days and pharmacokinetics was assessed
- A 21-day cumulative irritation study was performed in healthy male and female volunteers
- An 8-week Phase 2 study in male acne patients in which safety and efficacy were assessed
- The first clinical trial being proposed under the IND will be a 12-week Phase 2 study in acne patients with once or twice per day dosing. For the upcoming clinical trials CB-03-01 will be manufactured in a 0.1%, 0.5% and 1% cream formulation

Proof of Concept

- **Study Design CB-03-01/22**

A Phase 2, Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Dose Escalating Study to Evaluate the Safety and Efficacy of Cortexolone 17 α -Propionate Cream Applied Once or Twice-daily for 12 Weeks in Subjects with Facial Acne Vulgaris

- **Test Articles or treatment groups:**

- CB-03-01 Cream containing 0.1% cortexolone 17 α -propionate (BID)
- CB-03-01 Cream containing 0.5% cortexolone 17 α -propionate (BID)
- CB-03-01 Cream containing 1% cortexolone 17 α -propionate (QD*)
- CB-03-01 Cream containing 1% cortexolone 17 α -propionate (BID)
- Vehicle Cream (BID)

- **Study Population:** Male and female subjects 12-year or older with acne vulgaris (Grade 2 to 4 on Investigator's Global Assessment) on the face

- **Total Number of Subjects:** Approximately **360 subjects** (90 subjects per Cohort, where each Cohort includes 72 "active" treatment test article subjects and 18 vehicle test article subjects)

- **Number of Sites:** Approximately 10 sites in USA will participate in this study

Next Clinical development: CB-03-01/22

Investigator's Global Assessment (IGA)

Overall severity of acne using a five-point scale from 0= clear to 4= severe will be conducted at each visit. This is a static morphological scale that refers to a point in time and not a comparison to Baseline

0	Clear	Absence of active disease with no inflammatory or non-inflammatory lesions.
1	Almost Clear	Rare non-inflammatory lesions with no more than one small inflammatory lesion.
2	Mild	Greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only; no nodular lesions).
3	Moderate	Greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions but no more than one nodular lesion.
4	Severe	Greater than Grade 3; up to many non-inflammatory lesions and inflammatory lesions but no more than a few nodular lesions.

Lesion Counts

Inflammatory lesions (papules, pustules and nodules) and non-inflammatory lesions (open and closed comedones), including those on the nose, will be counted but recorded separately at each visit

Next Clinical development: CB-03-01/22

- **Study Endpoints**

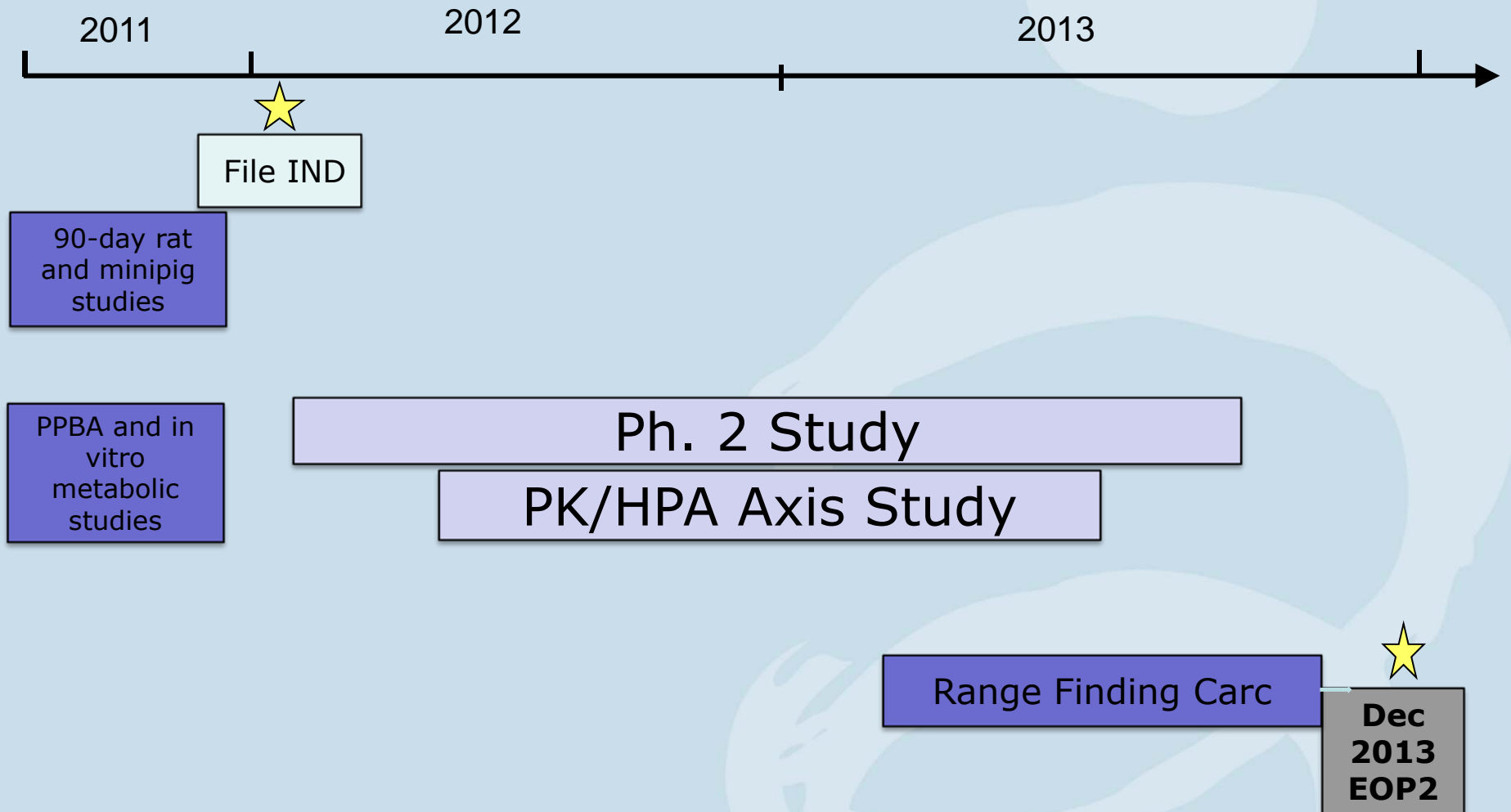
- **Primary Endpoints:**

- Proportion of subjects achieving success using the dichotomized IGA scale with success defined as a Week 12 score of “clear” or “almost clear” (IGA Score of 0 or 1) AND a two or more grade improvement from Baseline
- Absolute change from Baseline in inflammatory AND non-inflammatory lesion counts at Week 12

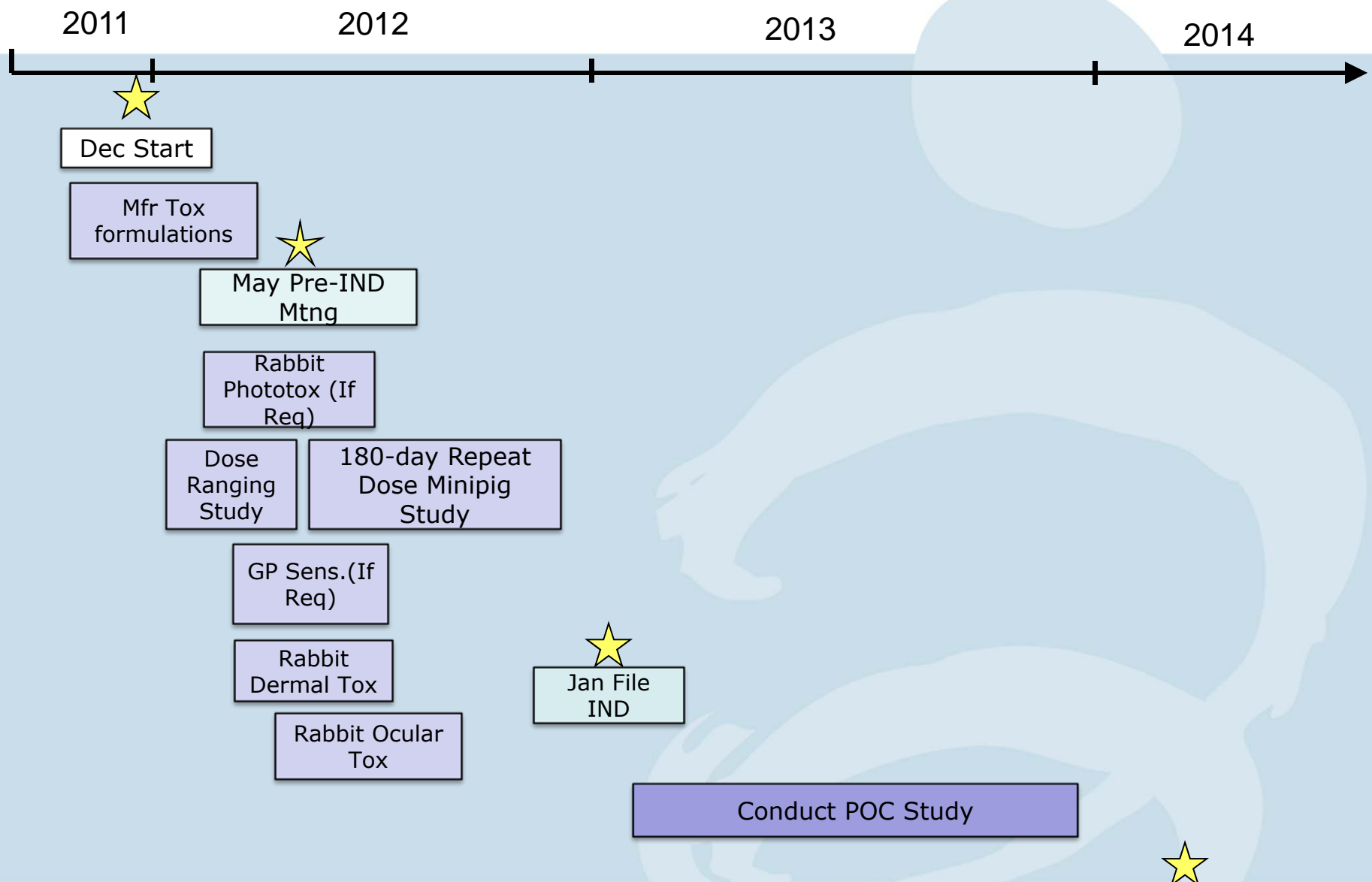
- **Secondary Endpoints:**

- Absolute change from Baseline in inflammatory AND non-inflammatory lesion counts at Week 8
- Percent change from Baseline in lesion counts at Weeks 8 and 12
- Proportion of subjects achieving success per the IGA at Week 8 (“success” as defined in the primary endpoints section)
- Proportion of subjects who are “clear” or “almost clear” (IGA Grade 0 or 1) at Weeks 4, 8 and 12

Key steps in Acne Studies



Key Alopecia Studies—Mar 2014 POC Report

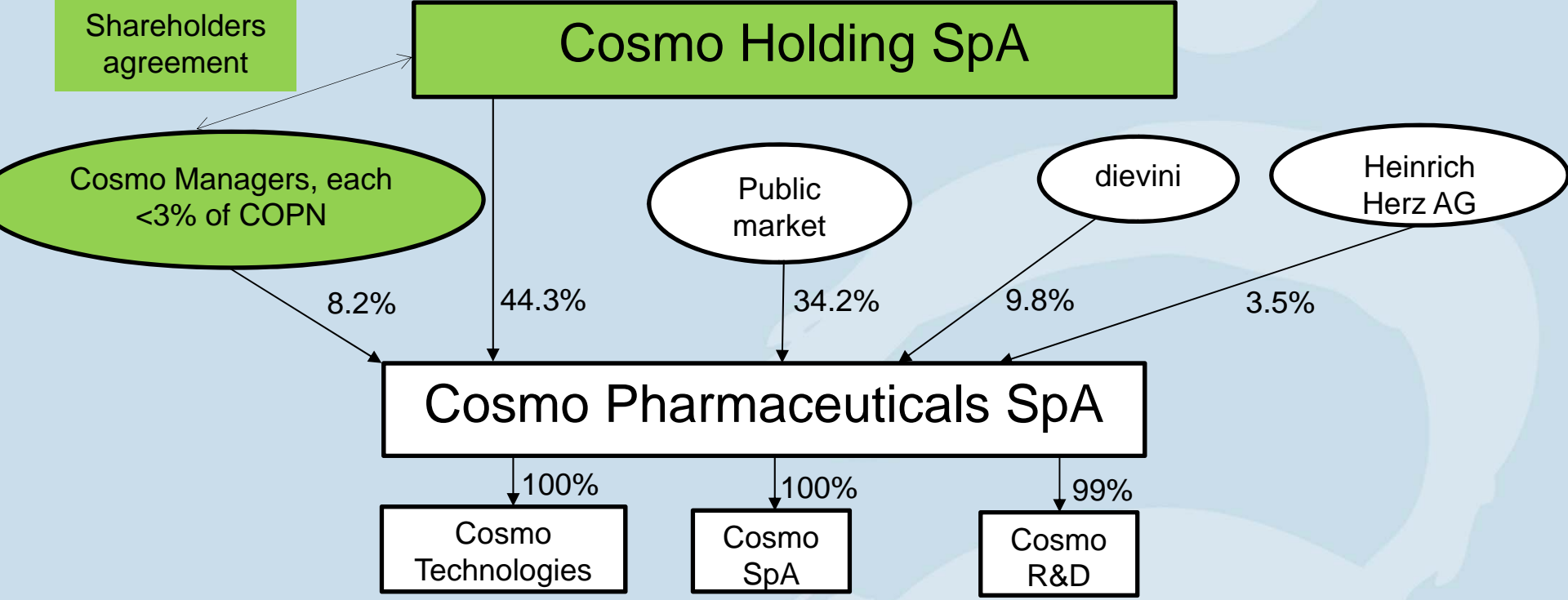


CB-03-01: way forward

- **Strategy**

- **We recognize we have need additional expertise to take this project forward**
- **Phase II will be developed together with an experienced party**
 - Numerous parties in data room
 - Discussions with numerous advisers & consultants
 - Decision to be made shortly

Cosmo group shareholding structure



Closing statements; M. Ajani

- **Practically all “promises” made at IPO have been fulfilled**
- **Three exciting new MMX products are likely to enter the market in next ~24 months.**
 - These will assure steady increase of revenues and EBIT as of 2013
- **The increasing expertise in the colon gives potential for further projects**
- **Own funds sufficient to fund all clinical programs**
 - The company has no debt
- **Cosmo will return all unneeded values to shareholders**

Contacts

Mauro Ajani; CEO

majani@cosmopharma.com

Dr. Chris Tanner; CFO and Head of Investor Relations;

ctanner@cosmopharma.com

Phone: 0039-02-9333'7453

Giuseppe Cipriano; COO

gqipriano@cosmopharma.com

Dr. Luigi Moro; CSO

lmoro@cosmopharma.com

www.cosmopharma.com

