



SANDOZ

Rimstar®: Pharmacokinetics and Clinical Trial Results

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a Novartis company



EU Approval & Bioequivalence Results

EU Approvals of Sandoz Fixed-Dose-Combinations

- **Rimstar® (HRZE), Rimcure® (HRZ), Rimactazid® (HR)**

- **Mutual Recognition Procedures SE/H/307-309 Approvals (MRP day 90): March 6, 2003**

BE; DK; ES; FI; FR; IRL; IT; NL; NO; UK

- **Bibliographic applications**

Article 10 (1) (a) (ii) of Directive 2001/83/EC:

„constituent(s) of a medicinal product have a **well established medicinal use**, with recognised efficacy and an acceptable level of safety ... (This legislation applies to any medicinal product, particularly where there is no original/reference medicinal product to which essential similarity can be claimed).“

- **Supportive Bioequivalence Studies (2-FDC, 3-FDC, 4-FDC)**

Rimstar® 4-FDC Bioequivalence Study - Methods

- Performed at **Dept Pharmacology, University Cape Town** (Investigators: Drs H. McIlleron, P. Smith, D. Hawarden, G. Gabriels, PB. Fourie)
- **Open, randomized, cross-over, single dose** study with 7 days washout period, in 24 healthy volunteers
- **Blood samples** were drawn: within 1 hour prior to drug administration and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, and 24.0 hours after drug administration.
Further samples drawn at 36.0 and 48.0 hours for the determination of pyrazinamide concentrations.
- **Analytics:** Validated HPLC methods developed at UCT
- **BE parameters:** AUC_{0-t}, AUC_{0-inf} (90% CI: 80-125%);
C_{max} (90% CI: 75-133%)

Rimstar® Bioequivalence Study - Methods

Test: Rimstar® Fixed Dose Combination

4 tablets single oral dose

Rifampicin	Isoniazid	Pyrazinamide	Ethambutol
150 mg	75 mg	400 mg	275 mg
600 mg	300 mg	1600 mg	1100 mg

Reference:

Rimactane®	Isozid®	Rolab	Myambutol®
Rifampicin	Isoniazid	Pyrazinamide	Ethambutol
4 x 150 mg	3 x 100 mg	®	2 x 400 +
		3 x 500 mg	3 x 100 mg
600 mg	300 mg	1500 mg	1100 mg

Rimstar® Pharmacokinetic Results

		C_{max} (mg/l)	AUC_{0-t} (mg.h/l)	AUC_{0-inf} (mg.h/l)
<i>Rifampicin</i>	T	12.7 ± 3.97	63.5 ± 19.8	71.8 ± 25.3
	R	12.8 ± 4.41	62.0 ± 21.6	69.0 ± 26.4
<i>Isoniazid</i>	T	4.51 ± 1.57	20.6 ± 12.1	23.5 ± 12.5
	R	4.47 ± 1.82	19.5 ± 9.05	22.5 ± 9.43
<i>Pyrazinamide</i>	T	35.2 ± 8.71	459 ± 119	473 ± 125
	R	34.3 ± 9.39	471 ± 108	489 ± 115
<i>Ethambutol</i>	T	3.27 ± 0.79	13.4 ± 4.56	16.9 ± 6.59
	R	3.52 ± 0.89	14.5 ± 6.21	17.3 ± 7.72

Rimstar® Bioequivalence Results

		Point estimate	90% confidence interval T/R
<i>Rifampicin</i>	C_{\max}	100	88.3 - 114
	AUC_{0-t}	103	92.3 - 115
	AUC_{0-inf}	104	94.2 - 116
<i>Isoniazid</i>	C_{\max}	103	88.3 - 121
	AUC_{0-t}	98.4	83.5 - 116
	AUC_{0-inf}	98.4	83.6 - 116
<i>Pyrazinamide</i>	C_{\max}	103	95.4 - 111
	AUC_{0-t}	96.3	88 - 106
	AUC_{0-inf}	95.8	87.7 - 105
<i>Ethambutol</i>	C_{\max}	92.7	79 - 109
	AUC_{0-t}	91.5	77.3 - 108
	AUC_{0-inf}	96.9	81.3 - 116



Rimstar® Clinical Trial

Sandoz History of Multicenter GCP Phase III Trials

- Phase IIIb trials according to ICH-GCP for EU registration

Code	Title	Patients	Centers	Publication
AMOR 1/96	The AMOR study: a randomized, double-blinded trial of omeprazole versus ranitidine together with amoxicillin and metronidazole for eradication of Helicobacter pylori	456	27	European Journal of Gastroenterol Hepatology 2001, 13:685-691
AMX 1/96	Randomized, double blind, double-dummy study comparing the efficacy and safety of amoxicillin 1 g bd with amoxicillin 500 mg tds in the treatment of acute exacerbations of chronic bronchitis	395	12	Poster 9th ECCMID Berlin 1999 JAC 2001;47:67-76
AMX 1/97	Efficacy and Tolerance of Amoxicillin 30 mg/kg bid versus Amoxicillin 15 mg/kg tid in the Treatment of Acute Otitis Media (AOM) in Children	516	26	Oral presentation 40th ICAAC, Toronto 2000 (Abstract 1971)

Sandoz History of Multicenter GCP Phase III Trials

- **Symposium presentation at 8th Scientific Meeting of European Society of Chemotherapy, February 2001 (Madeira, Portugal):**

Planning clinical trials according to ICH Guidelines; Methodological requirements for trial design & ICH statistical principles

ICH E6 (CPMP/ICH/135/95) NfG on GCP (1996)

CPMP NfG on Evaluation of new antibacterial medicinal products (1997)

ICH E9 (CPMP/ICH/363/96) NfG on Statistical Principles for Clinical Trials (1998)

ICH E10 (CPMP/ICH/364/96) NfG on Choice of Control Group in Clinical Trials (2000)

CPMP Points to Consider on Switching between Superiority and Non-Inferiority (2000)

CPMP Points to Consider on Missing data (2001)

...

→ Approach to TB 4-FDC trial endpoints taking WHO/IUATLD definitions AND ICH principles into account

Comparison of two short-course regimens of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) given either as fixed-dose combination (4-FDC) or as single tablets (ST) in smear-positive pulmonary TB

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36th Union World Conference on Lung Health, October 18-22, 2005, Paris (PC-1341-22)



Introduction

Introduction

- Tuberculosis remains a major and growing problem in every region of the world
- **Adequate treatment** is one of the most important steps in preventing drug resistance
- The treatment of smear-positive pulmonary tuberculosis (PTB) patients with **short-course multidrug chemotherapy** for 6 or 8 months is regarded as the cornerstone of a modern approach of TB treatment
- Recommendations for FDCs have been founded on valid scientific principles but **practical experience with 4-FDCs is limited**

Introduction

The objective of the present study was to compare the

- **efficacy**
- **safety and**
- **acceptability**

of two short-course regimens of HRZE given either as 4 FDC tablets or as single preparation tablets in patients with newly diagnosed PTB.



Material and Methods

Material and methods

- **Type of trial:**

Randomised, multinational, multicentre, open trial in two parallel groups

- **26 Study centres:**

Egypt, India, Pakistan, Thailand and Philippines

- This trial was conducted in accordance with **ICH-GCP standards** and the Drug Law of the respective country
- Protocol approved by each local EC informed consent obtained for each patient before inclusion



Inclusion criteria

Male and female patients with newly diagnosed pulmonary tuberculosis who fulfill the following criteria

- Age of 15 or older
- At least **two sputum specimens positive** for acid-fast bacilli (tubercle bacilli) on **direct smear microscopy** or **one sputum specimen positive** for acid-fast bacilli (tubercle bacilli) on direct smear microscopy **and posteroanterior chest X-ray consistent with pulmonary tuberculosis** as determined by a clinician
- No previous anti-tuberculosis therapy or less than one month of previous anti-tuberculosis therapy
- Written informed consent and willingness to comply with the protocol

Exclusion criteria

- Body weight below 30 kg (below 50 kg in Egypt)
- Known or suspected **hypersensitivity** to rifamycins and/or to isoniazid and/or to pyrazinamide and/or to ethambutol hydrochloride and/or to any of the excipients
- History of drug induced hepatitis
- Suspected or known cases of **acute and chronic liver diseases** regardless of their origin
- Suspected or known cases of **renal failure**
- Suspected or known cases of peripheral **optic neuritis**
- Acute **gouty arthritis** (on clinical diagnosis) or history of gout
- TB – **Meningitis**

Exclusion criteria

- Any condition (except HIV infection) that may prove fatal during the study period (for example metastatic cancer)
- **Poor general condition** of patient requiring additional measures to ensure survival
- **Immunosuppressive therapy** (e.g. corticosteroids) during the whole study period
- History of **alcohol or drug abuse** likely to lead to uncooperative behaviour
- History of **psychiatric illness** likely to lead to uncooperative behaviour
- Pregnancy

Treatments

Test group

Initiation phase - first 2 months:
(HRZE: 75/150/400/275 mg per tablet) daily

Rimstar® 4-FDC



Continuation phase of 4 months:
(HR: 75/150 mg) daily

Rimactazid®

→ Posology according to WHO and IUATLD recommendations:

Body weight	Tablet number
30-37	2
38-54	3
55-70	4
>70	5

Treatments

Control group

Initiation phase - first 2 months:

Single preparations of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol

Continuation phase of 4 months:

Single preparations of Rifampicin and Isoniazid

[Rifampicin and Isoniazid to be administered also as 2-FDC combination tablets].

→ Posology according to national treatment standards of each respective country.

Randomisation - Concealment

- **Randomisation** was **generated by computer** by an independent central randomisation institute (block size confidential).
- Adequately labelled and packed trial medication batches, together with **sealed serially numbered opaque randomisation envelopes** were provided to each participating centre.
- The control group was treated with medication of local/national suppliers of mono-substance/2-FDC drugs.

Efficacy and patient assessments

EXAMINATION	Day 0	M 2	M 4	EOT M 6	FU M 9	FU M 12
Posteroanterior chest X-ray	x			x		
Sputum smear microscopy	x	x	x	x	x	x
Assessment of regimen by the patient		x		x		
Assessment of compliance	x	x	x	x		
Assessment of adverse events		x	x	x	x	x

Efficacy and patient assessments

Sputum smear microscopy (efficacy recording)

- after 2 months of therapy (end of intensive phase)
- after 4 months of therapy (during continuation phase)
- after 6 months (at the end of the continuation phase, EOT)
- after 9 and 12 months of initiation of treatment (follow-up)

Response at EOT was assessed as

- **(i) cure** (sputum smear negative at EOT and month 4)
- **(ii) failure/relapse** (sputum smear still or again positive after 4 and/or 6 months of treatment)

Response at month 12 was assessed according to EOT definitions as:

- **(iii) cure** (sputum smear negative in a patient cured at EOT)
- **(iv) relapse** (patient cured at EOT and sputum smear again positive at months 9 or 12).

Efficacy and patient assessments

Chest X-Ray

→ posteroanterior chest X-ray at EOT to assess X-ray improvement to baseline

Overall patient assessment

- Overall acceptability of regimens regarding number, size and taste of tablets assessed at month 2
- Overall tolerance and treatment success assessed at EOT

Patient populations

⇒ **Intent-to-treat (ITT)** = all randomized patients receiving at least one dose of medication

A sensitivity analysis was performed, imputing all missing data in the ITT population as failure.

⇒ **Intent-to-treat complete cases (ITTcc)** = all randomized patients receiving at least one dose of medication and having a valid sputum smear evaluation at EOT

⇒ **Per protocol (PP)** = all ITT patients, completing the treatment, being adequately compliant to the treatment regimen (missed intake of medication ≤ 3 consecutive days in the initial and/or ≤ 7 consecutive days in the continuation phase), receiving correct daily dosage (according to body weight), and not violating the protocol in any way liable to influence efficacy outcome.

Patient populations

Population for efficacy analysis at follow up

- **Relapse population** = all subjects within the ITTcc and PP population being sputum smear negative at EOT and having at least one post-EOT evaluation of sputum smear (at month 9 and/or month 12).

Sample size and statistical methods

Sample size estimation

$\alpha = 0.05$ (one tailed); power = 90 %

Sputum smear conversion rate at EOT

- ➔ expected EOT success rate (single preparations): 85%
- ➔ $\delta = 10\%$ (lower limit of 95 % CI around the difference single-4-FDC not below -10%)
- ➔ N = 229 evaluable per group (N = 286 planned, 25% expected drop-out rate) for primary efficacy

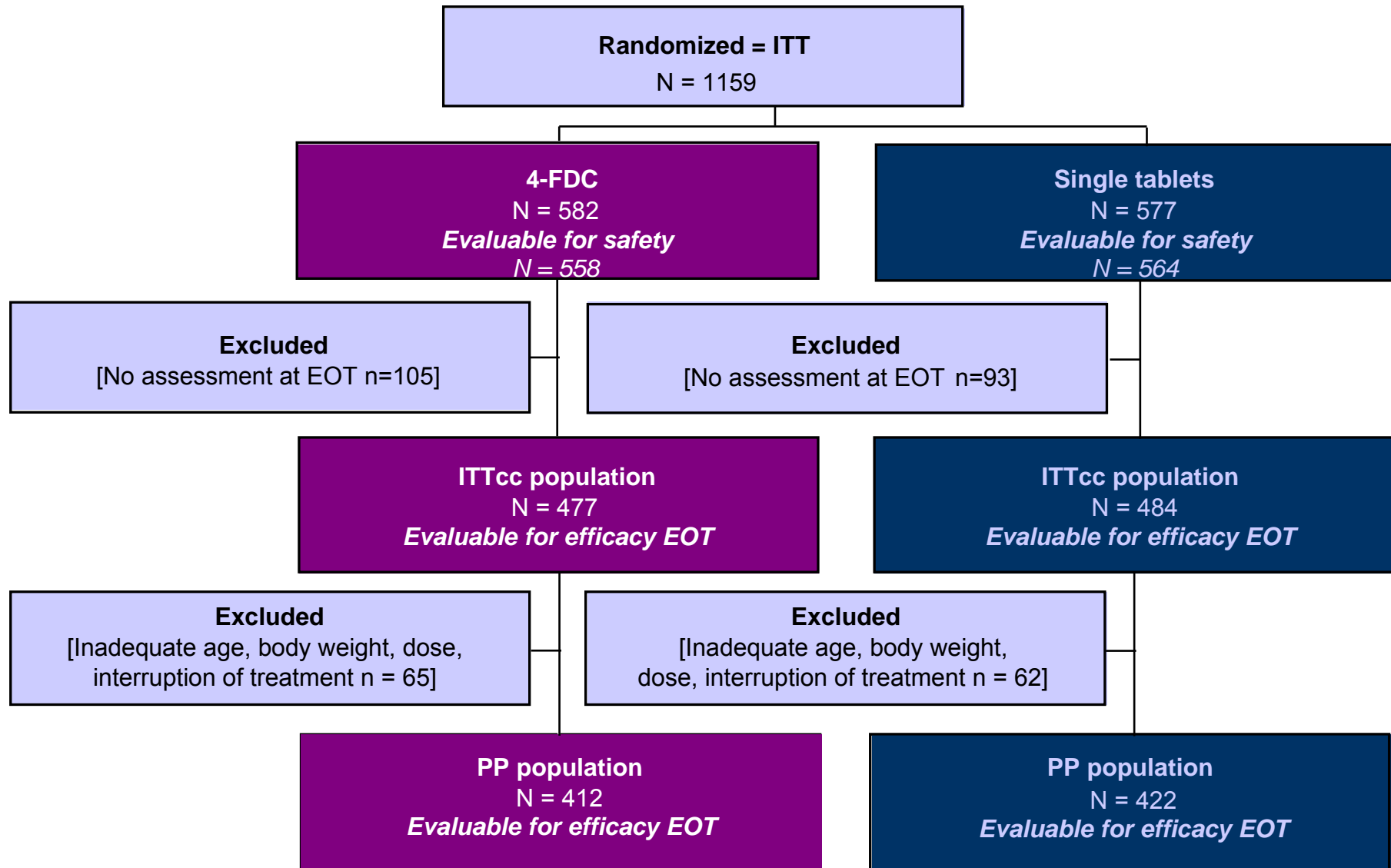
Relapse rate

- ➔ expected relapse rate (single preparations): 4%
- ➔ $\delta = 4\%$
- ➔ N = 439 evaluable per group (N = 592 planned, 35% expected drop-out rate) for relapse rate



Results

Disposition of study patients



Patient characteristics

Nationality	ITT	ITTcc	PP	Total
Egypt	200 (17.3)	168 (17.5)	154 (18.5)	200 (17.3)
India	289 (24.9)	231 (24.0)	224 (26.9)	289 (24.9)
Pakistan	180 (15.5)	162 (16.9)	133 (15.9)	180 (15.5)
Thailand	291 (25.1)	249 (25.9)	222 (26.6)	291 (25.1)
Philippines	199 (17.2)	151 (15.7)	101 (12.1)	199 (17.2)
Total	1159 (100)	961 (100)	834 (100)	1159 (100)

Demographic data

Characteristics	ITT		PP	
	4-FDC	Single tablets	4-FDC	Single tablets
Gender (No. [%])				
M	391 (67.2)	406 (70.4)	276 (67.0)	297 (70.4)
F	191 (32.8)	171 (29.6)	136 (33.0)	125 (29.6)
Age [mean± SD] years	37.4 ± 15.3	36.1 ± 14.6	36.4 ± 14.6	35.5 ± 14.4
Height [mean± SD] cm	161.5 ± 9.9	161.8 ± 8.9	162.2 ± 9.7	162.4 ± 8.9
Weight [mean± SD] kg	50.3 ± 11.5	49.9 ± 10.3	50.1 ± 9.9	50.5 ± 10.4

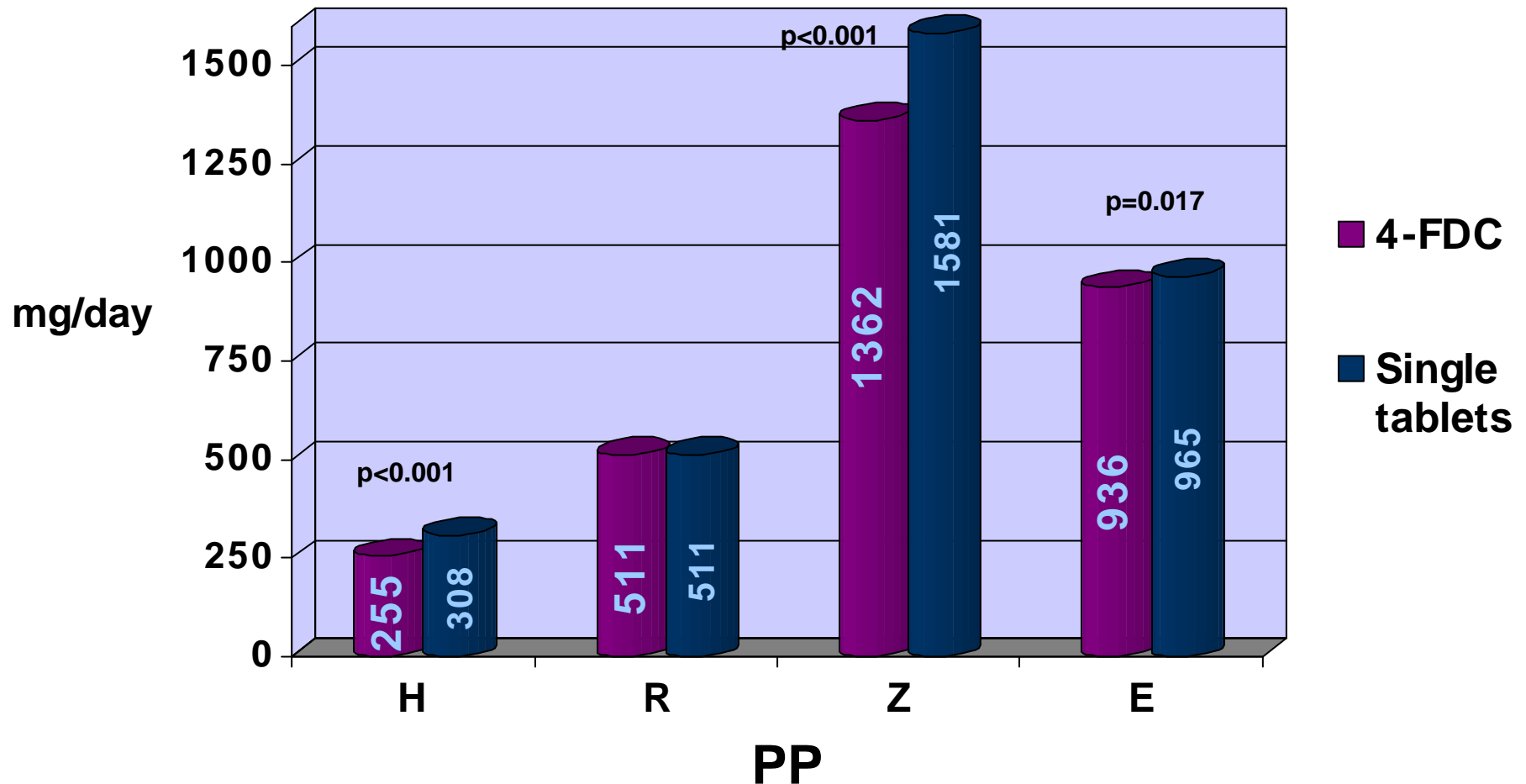
Clinical characteristics at baseline

Characteristics	ITT		PP	
	4-FDC	Single tablets	4-FDC	Single tablets
Previous treatment* of TB	109 (18.7)	112 (19.4)	74 (18.0)	66 (15.6)
Lung right affected severe	103 (17.7)	93 (16.1)	72 (17.5)	63 (14.9)
Lung left affected severe	92 (15.8)	96 (16.6)	58 (14.1)	67 (15.9)

*80% of patients were treated \leq 2 weeks

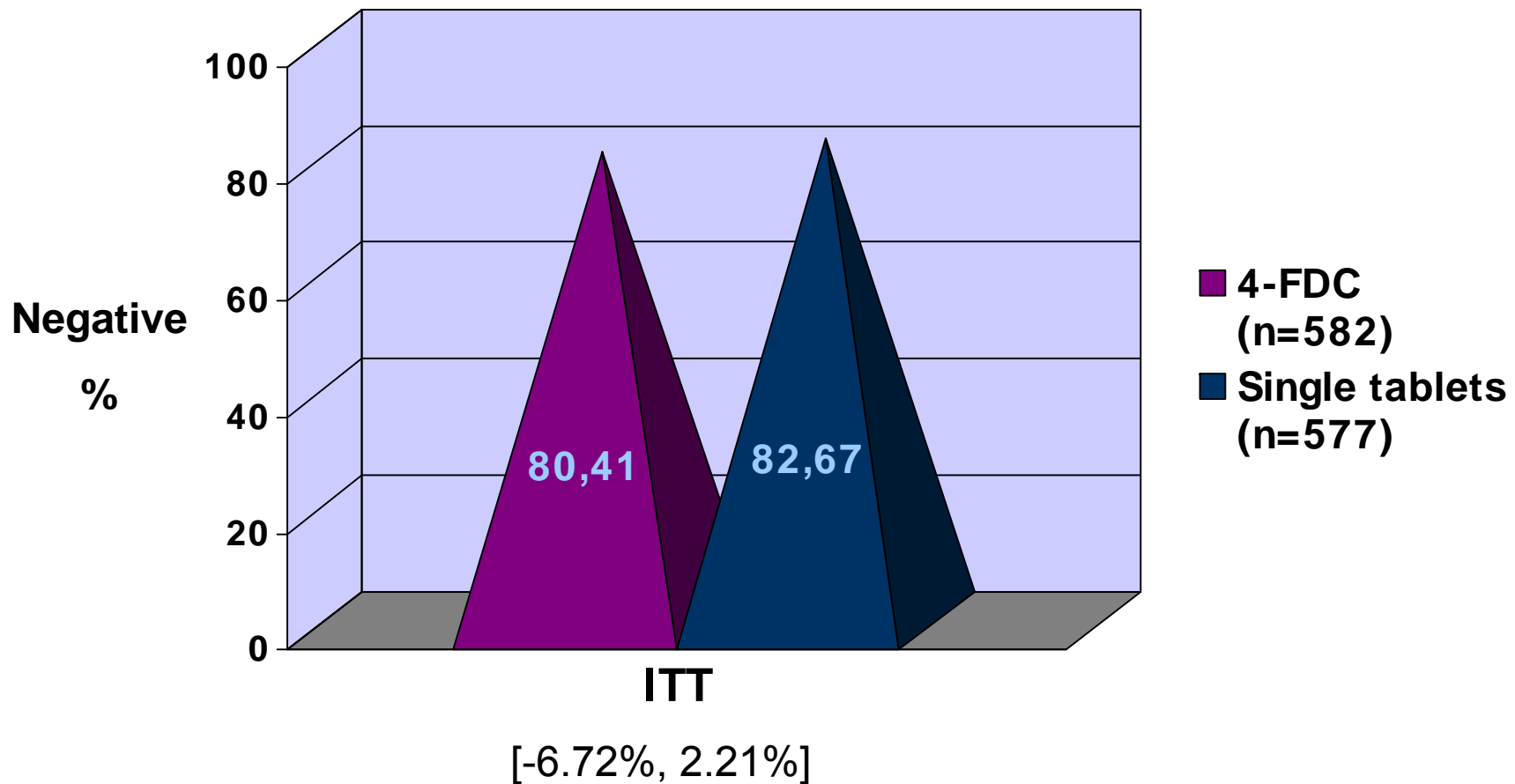
Dosage regimen

Mean daily doses during initiation phase



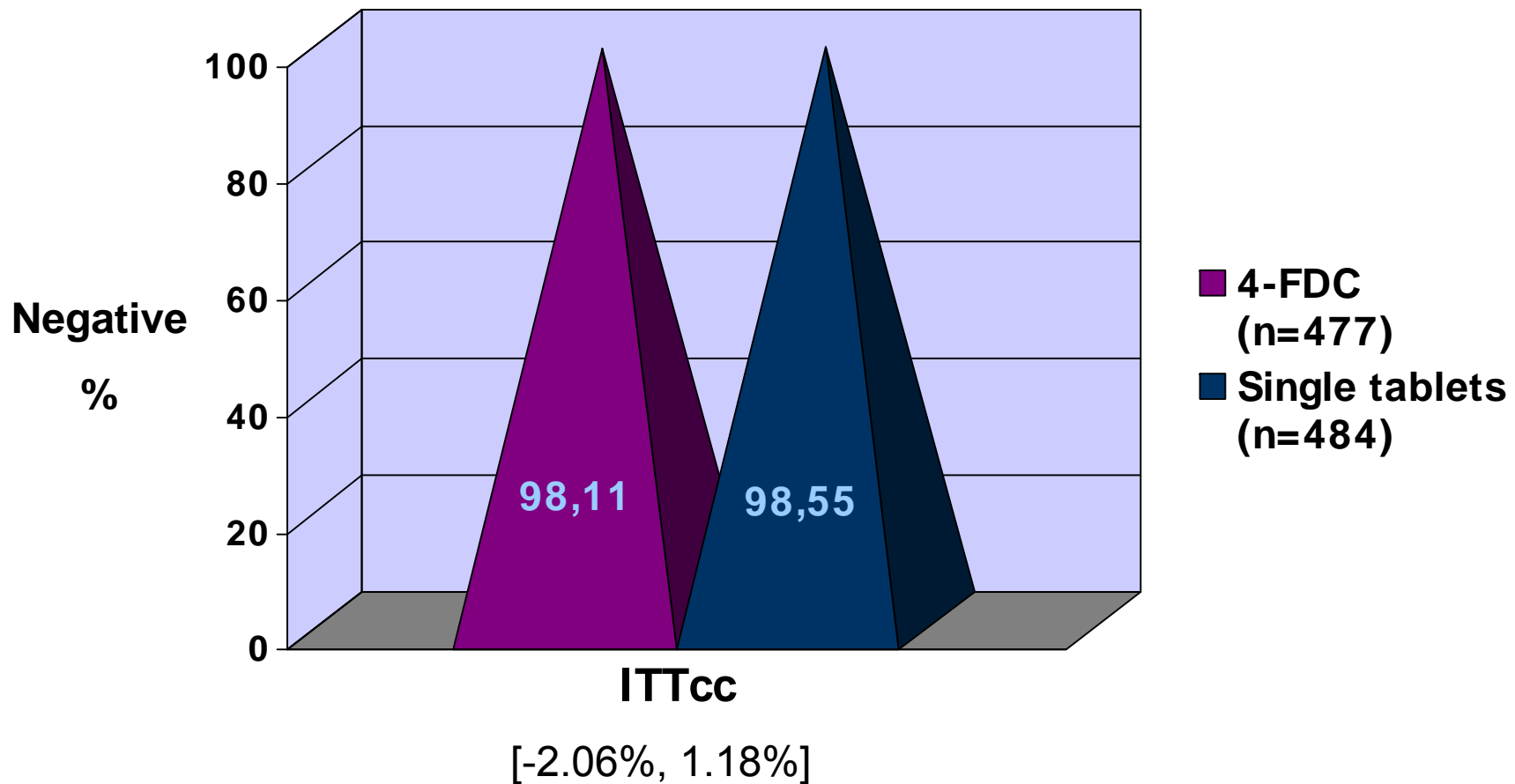
Bacteriological outcome

Bacteriological cure – at EOT



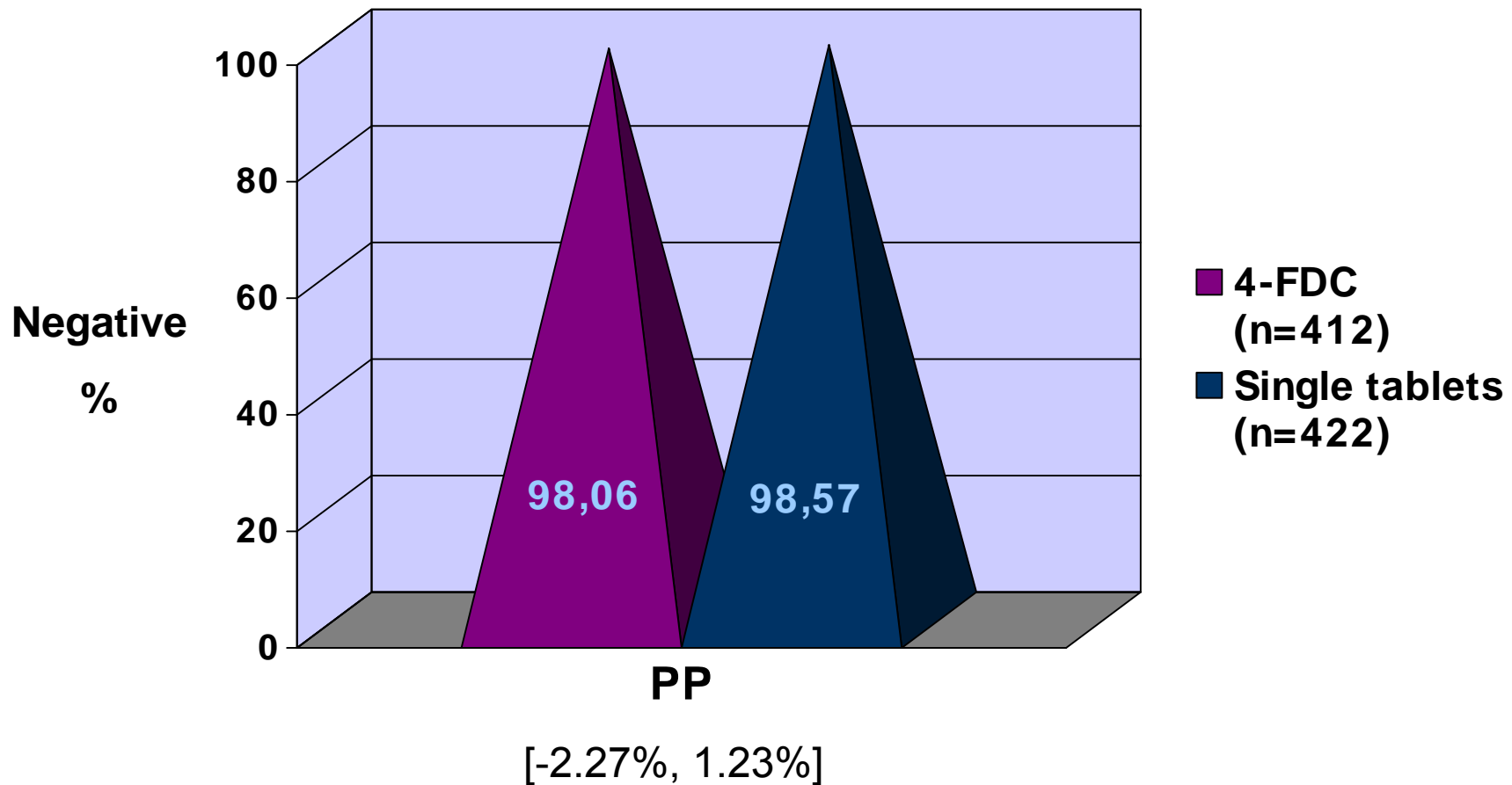
Bacteriological outcome

Bacteriological cure – at EOT



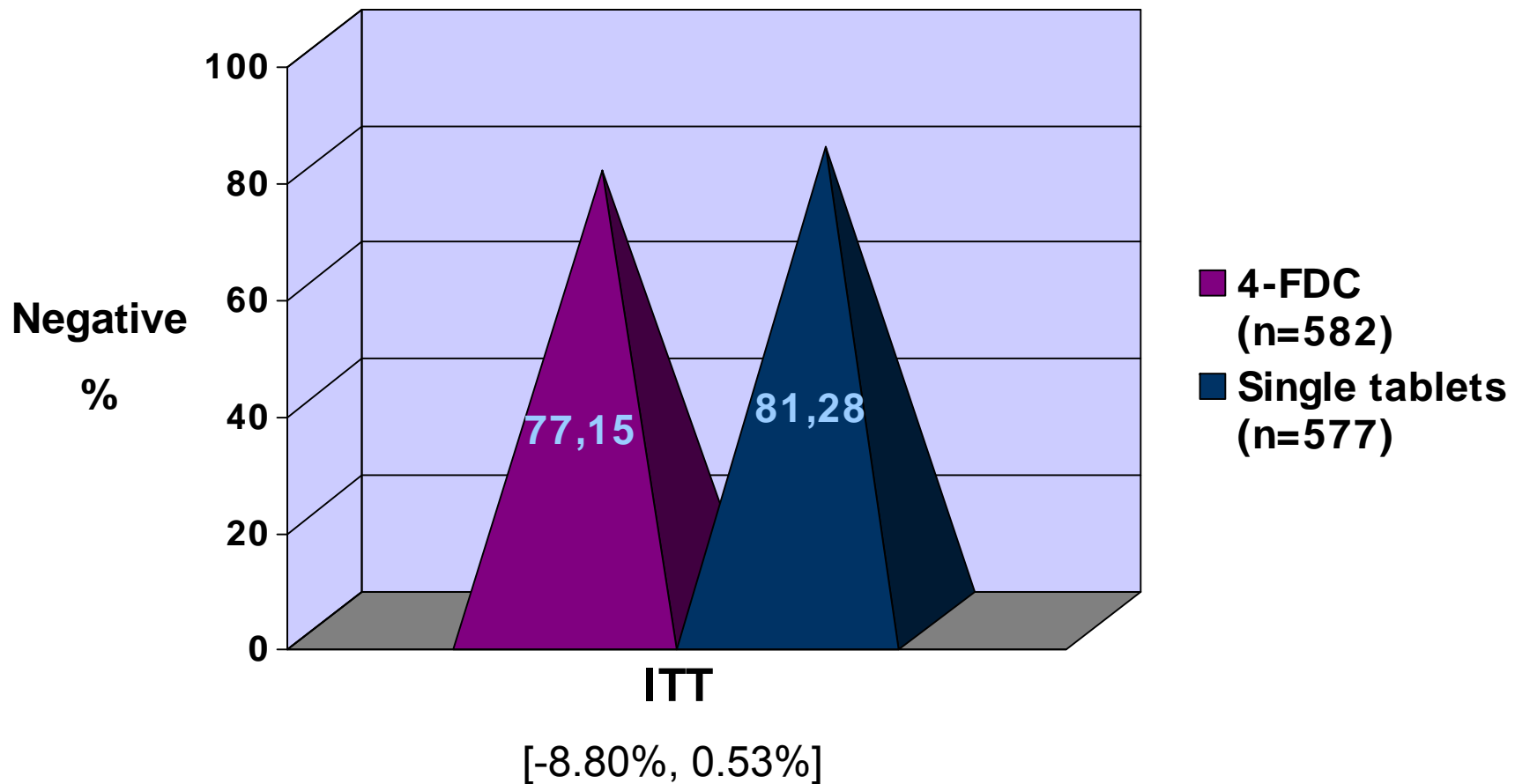
Bacteriological outcome

Bacteriological cure – at EOT



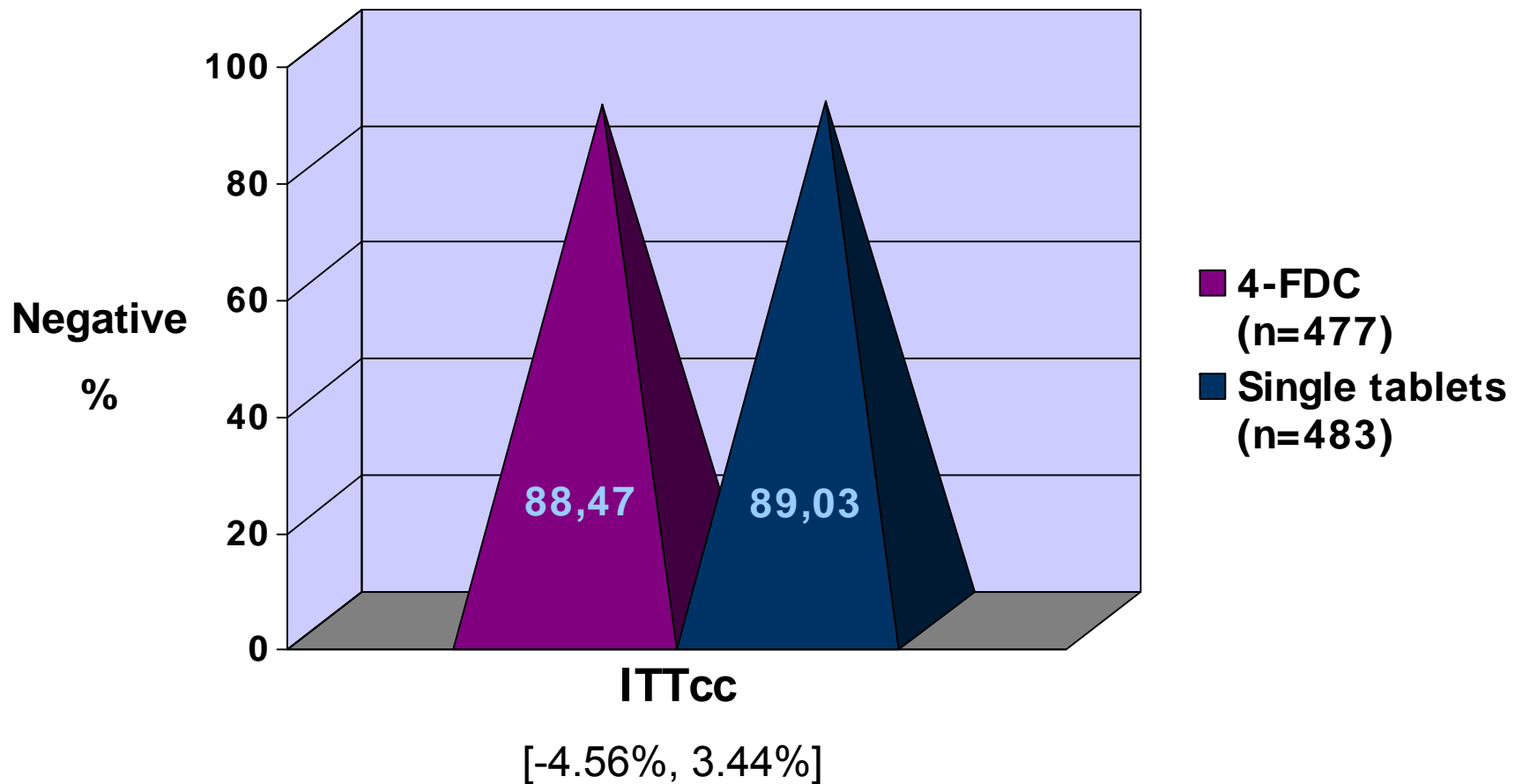
Bacteriological outcome

Bacteriological cure – at month 2



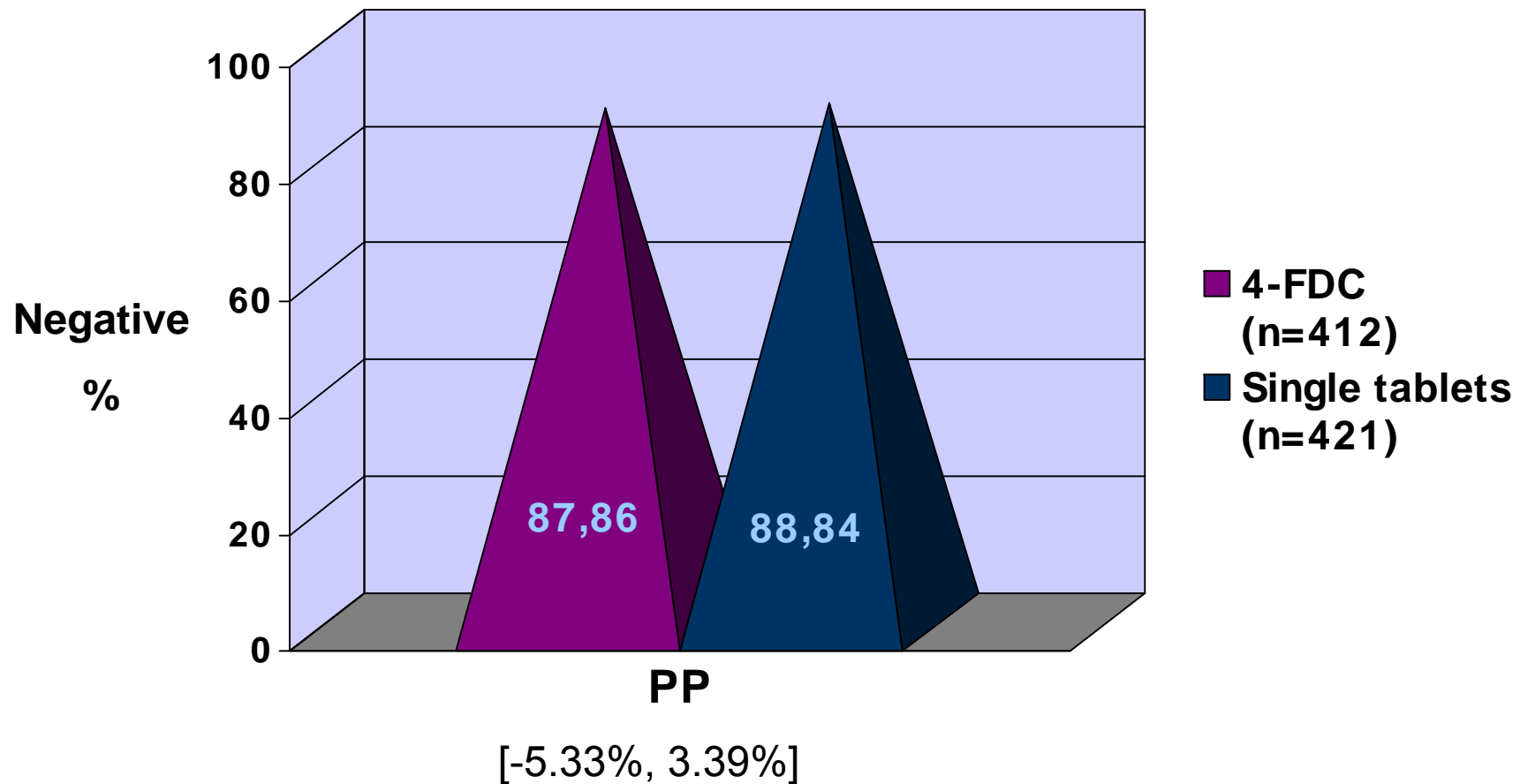
Bacteriological outcome

Bacteriological cure – at month 2



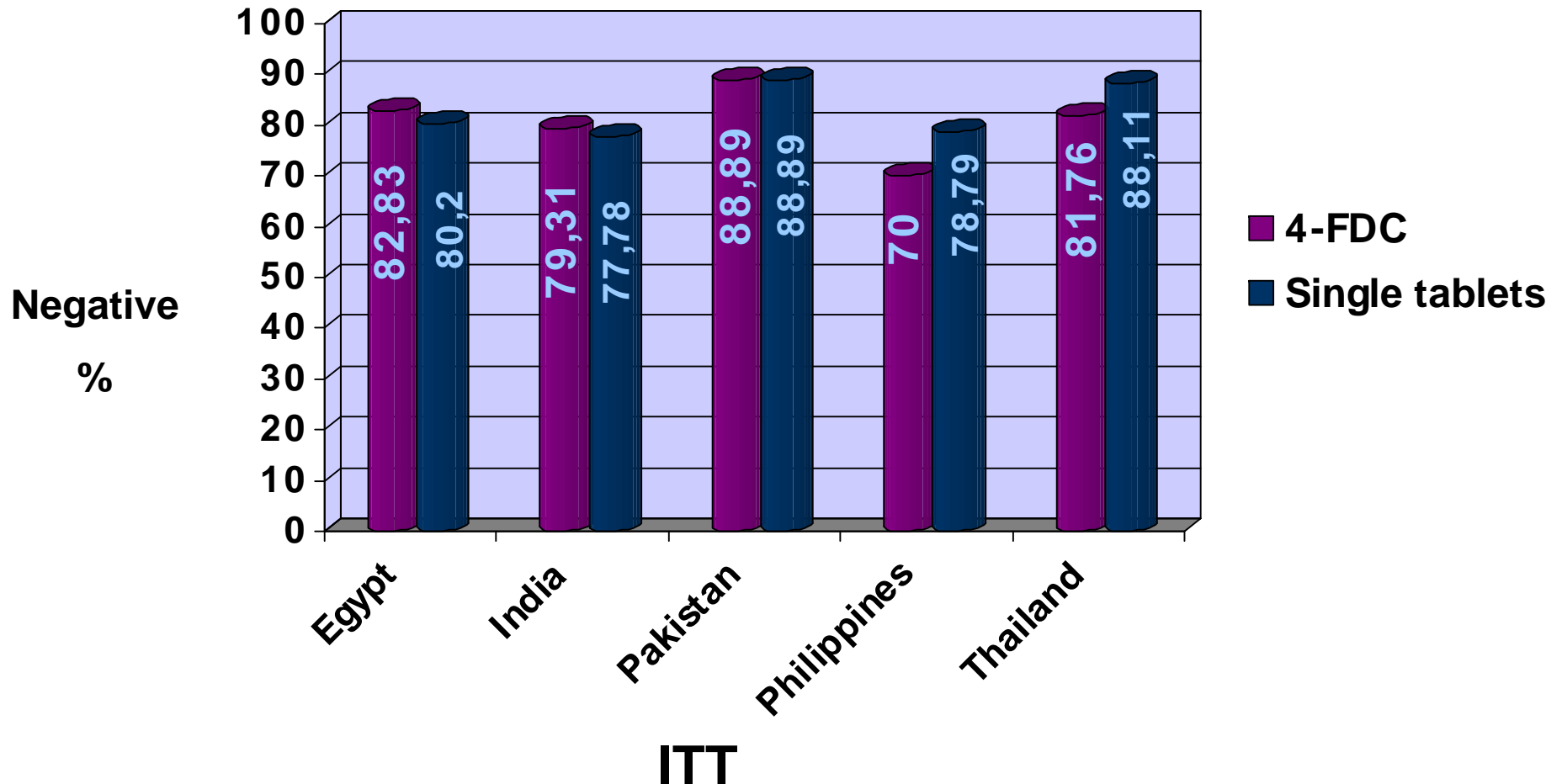
Bacteriological outcome

Bacteriological cure – at month 2



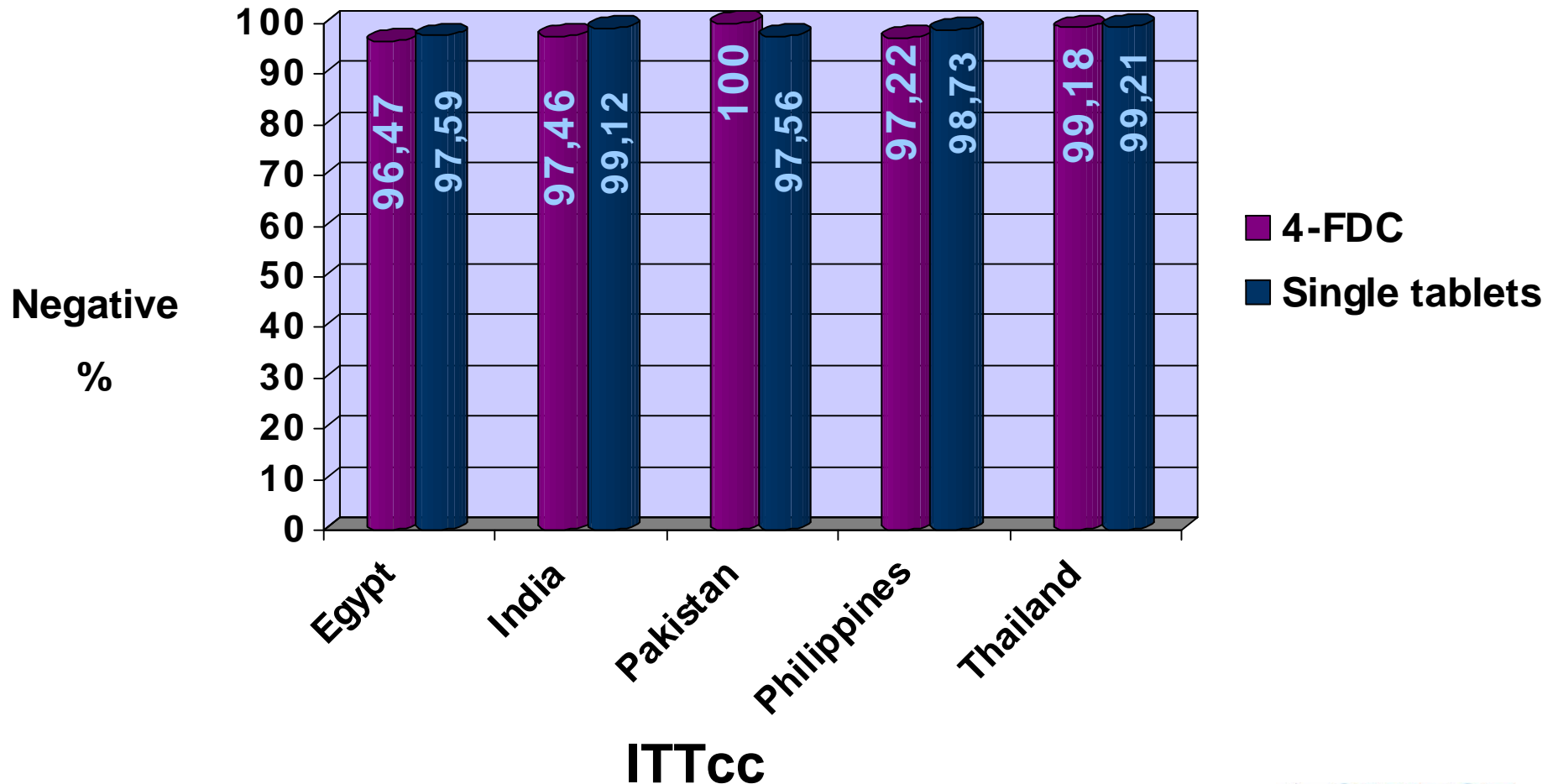
Bacteriological outcome

Country results: Bacteriological cure at EOT



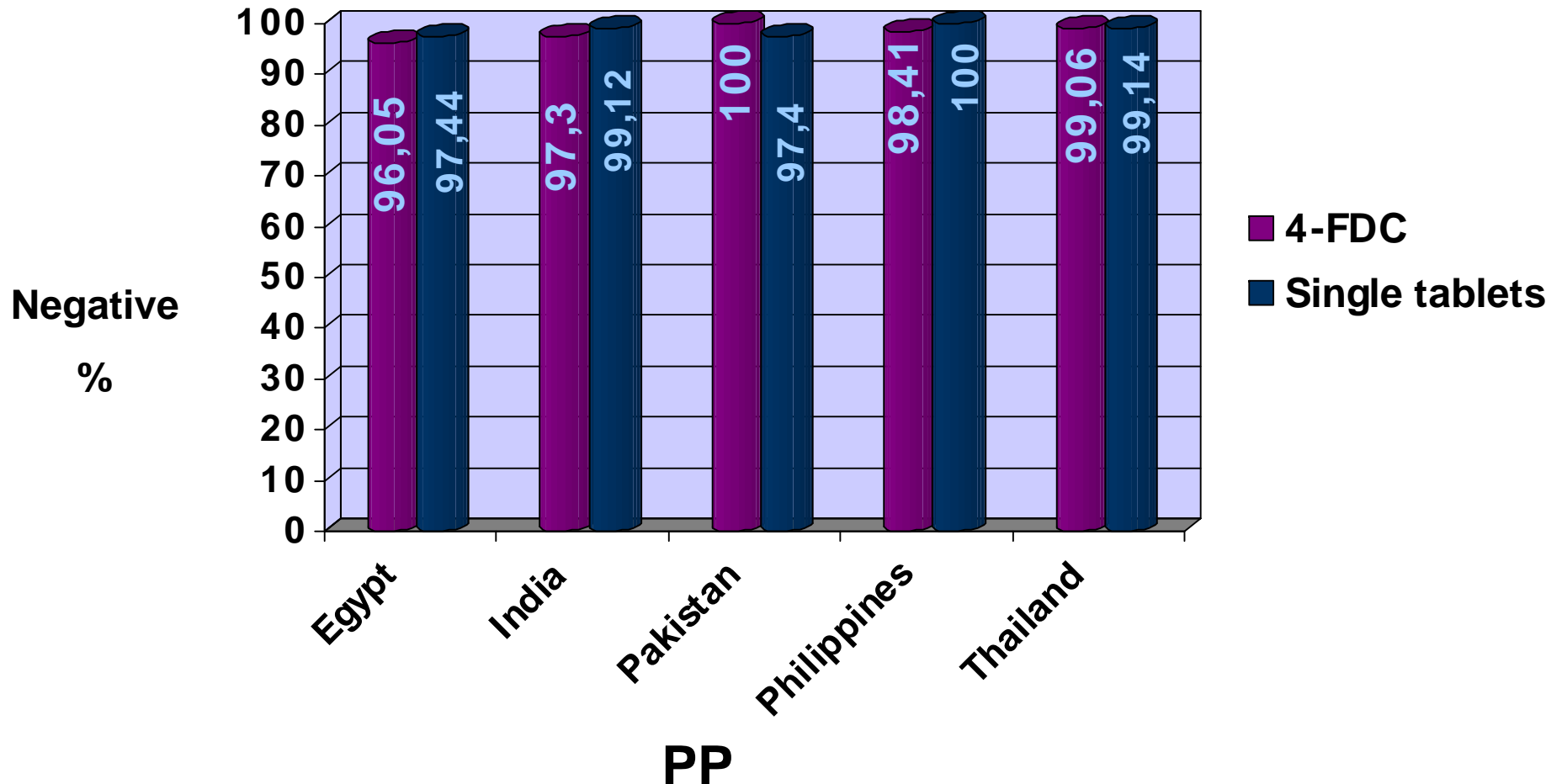
Bacteriological outcome

Country results: Bacteriological cure at EOT



Bacteriological outcome

Country results: Bacteriological cure at EOT

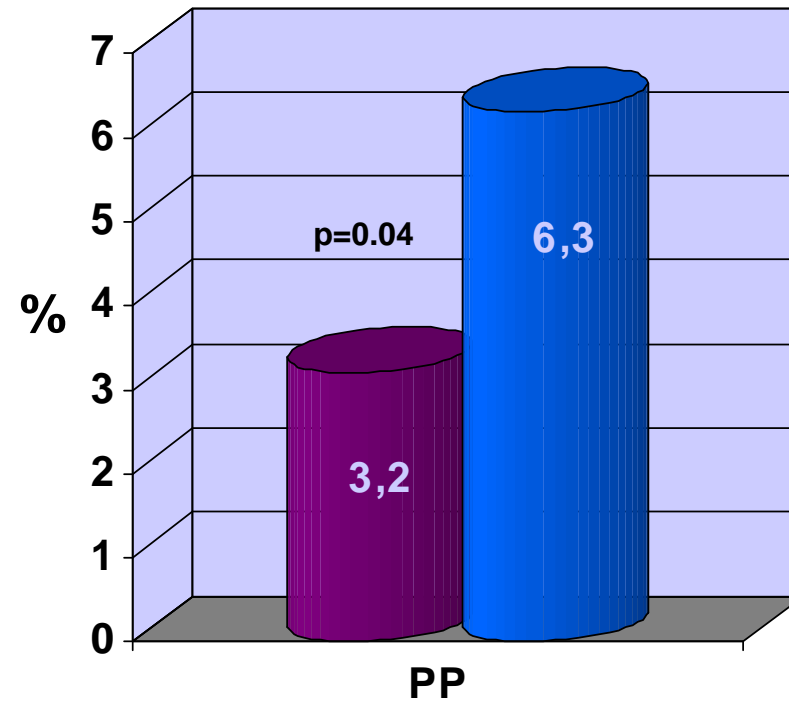
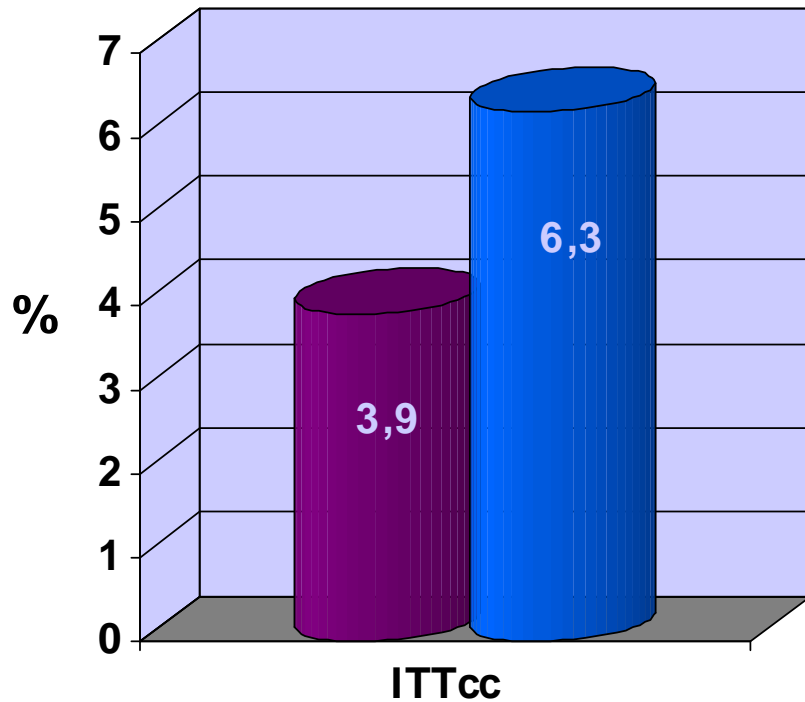


X-ray improvement

X-ray improvement to baseline 4 examination	ITTcc		PP	
	4-FDC	Single tablets	4-FDC	Single tablets
very good	253 (53.4)	249 (52.2)	224 (54.8)	222 (53.4)
satisfying	201 (42.4)	221 (46.3)	171 (41.8)	189 (45.4)
unimproved	15 (3.2)	7 (1.5)	10 (2.4)	5 (1.2)
worse	5 (1.1)	0	4 (1.0)	0

Overall patient assessments

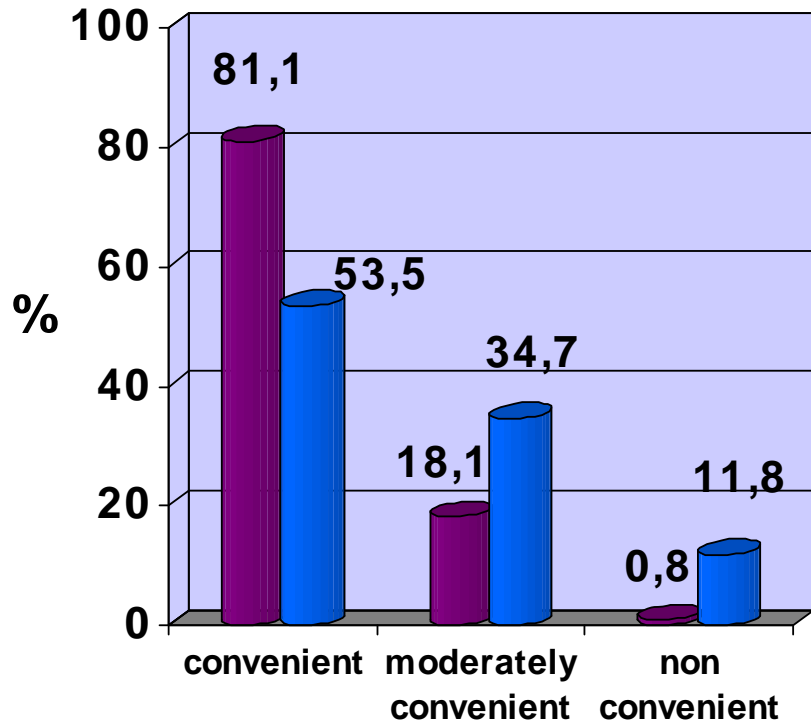
Problems on swallowing – after 2 months treatment



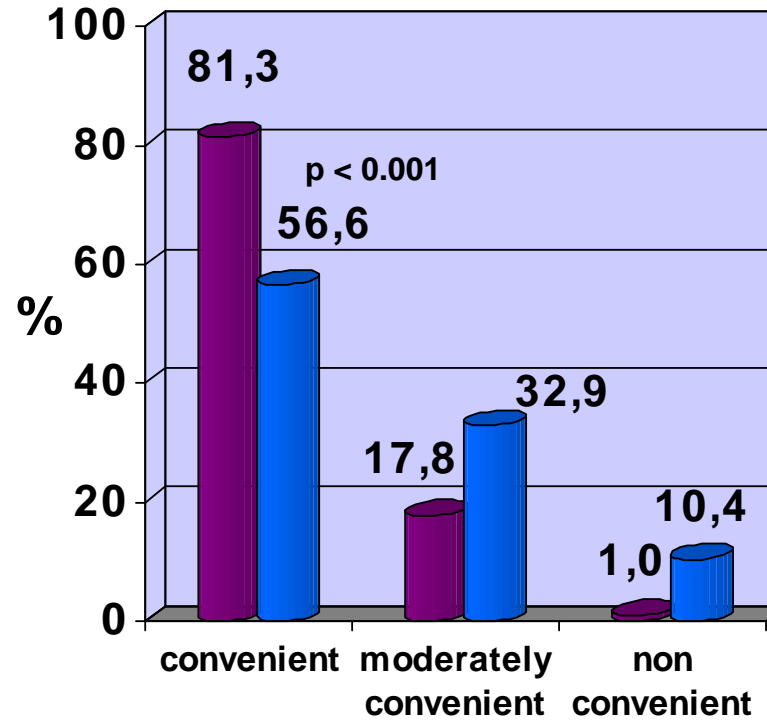
■ = 4-FDC
■ = Single tablets

Overall patient assessments

Acceptability of number of tablets – examination 2



ITTcc



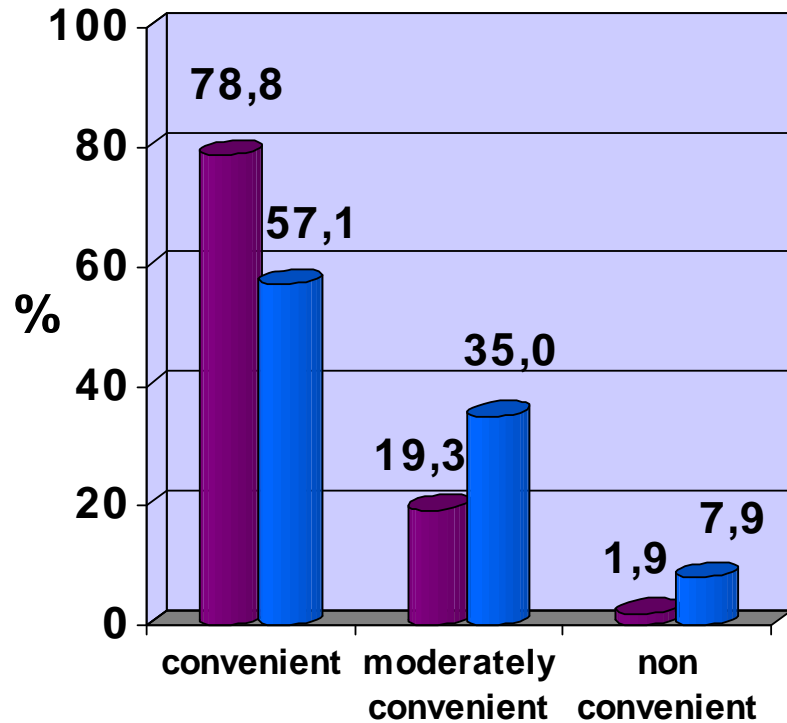
PP

■ = 4-FDC

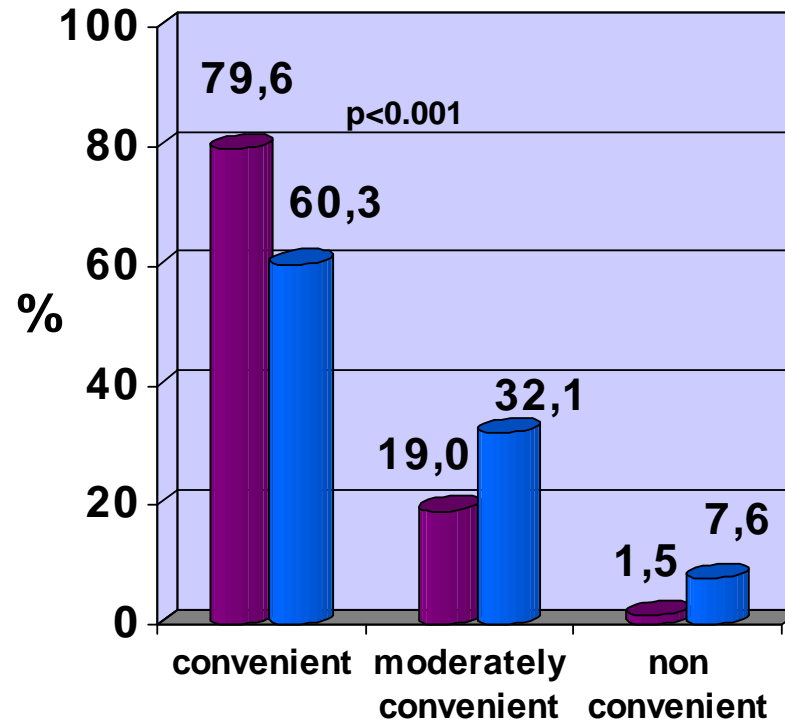
■ = Single tablets

Overall patient assessments

Acceptability of taste of tablets – examination 2



ITTcc

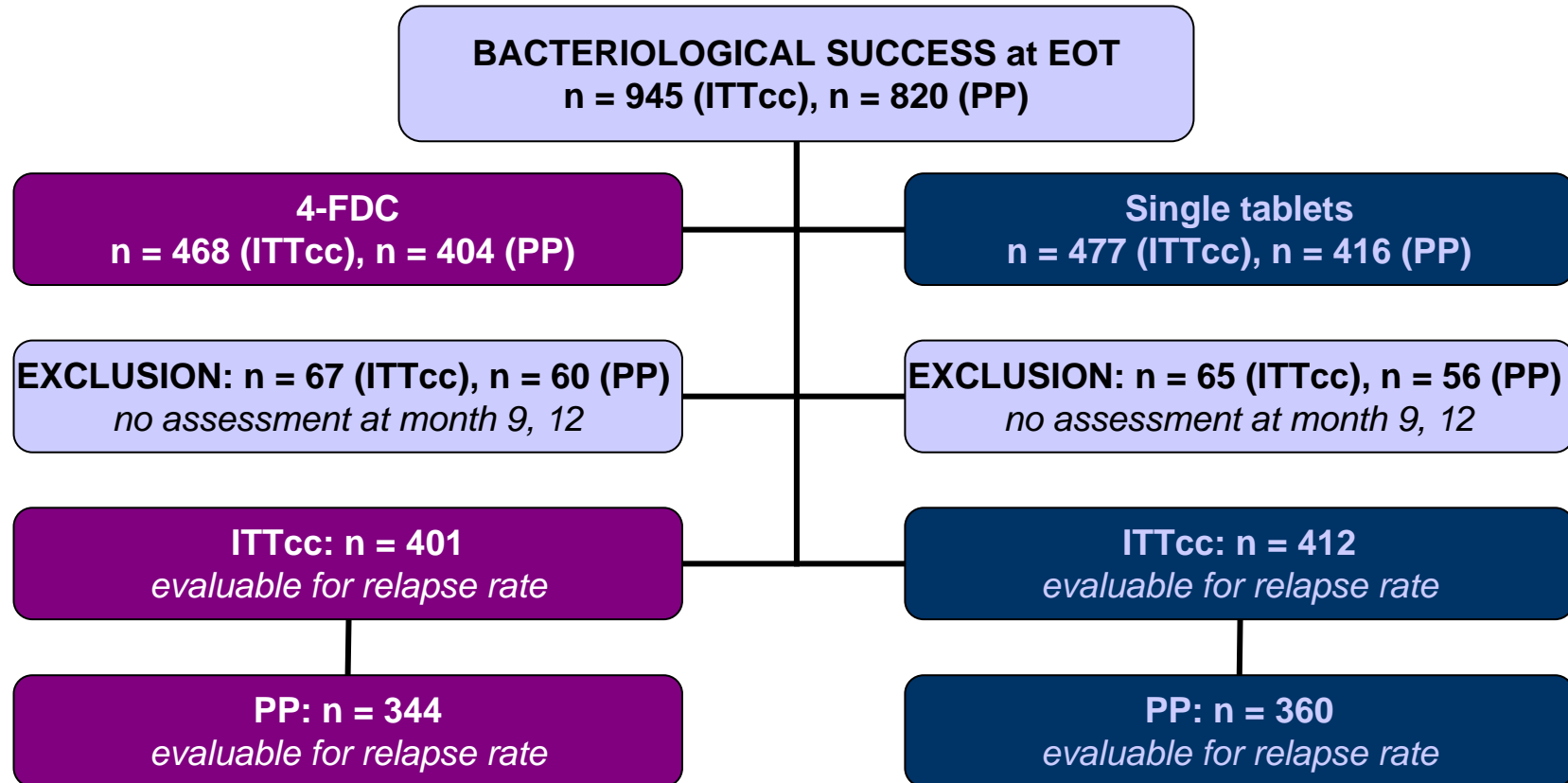


PP

■ = 4-FDC

■ = Single tablets

Disposition of relapse population



Outcome at Follow-Up

Relapse rates	ITTcc		PP	
	4-FDC	Single tablets	4-FDC	Single tablets
Total	7 1.75% (7/401)	4 0.97% (4/412)	6 1.74% (6/344)	3 0.83% (3/360)
	[95% CI: -0.82, 2.37]		[95% CI: -0.76, 2.58]	

Relapse rates - country results

Relapse	ITTcc		PP	
	4-FDC	Single tablets	4-FDC	Single tablets
Egypt	2 (2.44%)	0	2 (2.74%)	0
India	1 (1.37%)	0	1 (1.41%)	0
Pakistan	1 (1.28%)	2 (2.56%)	0	2 (2.70%)
Philippines	1 (1.75%)	2 (2.94%)	1 (2.00%)	1 (3.03%)
Thailand	2 (1.80%)	0	2 (2.11%)	0
Total	7 (1.75%)	4 (0.97%)	6 (1.74%)	3 (0.83%)

Adverse events in patients evaluable for safety

Adverse event	4-FDC	Single tablets
Total no. of patients evaluable for safety	558	564
No. of patients with AEs (%)	129 (23.1) ^a	117 (20.7)
No. of patients with drug-related AEs	105 (18.8) ^b	94 (16.7)
Total number of AEs (% of total patients)	225 (40.3) ^c	203 (36.0)
No. of drug-related AEs (% of total AEs)	165 (73.3) ^d	129 (63.5)
Gastrointestinal AEs (nausea, vomiting,...)	43 (26.1)	43 (33.3)
Skin disorders (pruritus, rash,...)	40 (24.2)	30 (23.3)
Musculo-skeletal disorders (joint pain,...)	20 (12.1)	22 (17.0)
Liver and biliary system (jaundice, hepatitis,..)	14 (8.5) ^e	21 (16.3)
Body as a whole (headache, fever,...)	29 (17.6) ^f	5 (3.9)

^a [-2.4%; 7.2%]; ^b [-2.3%; 6.6%]; ^c [-1.35%; 10%]; ^d p = 0.03; ^e p = 0.031; ^f p < 0.001;

Adverse events

- **In 47* patients Serious AEs were reported**
 - 31 in the 4-FDC group versus 18 in the single tablets group**
 - **In 27* patients serious events were considered to be related to the study medication**
 - 16* in the 4-FDC group versus 11 in the single tablets group**
- *in two patients, SAEs had been downgraded by drug safety unit at follow up
- **40 patients discontinued therapy prematurely because of AEs**
 - 25 in the 4-FDC group**
 - 15 in the single tablets group**
 - **15 deaths occurred, 2 of them (2 FDC) considered drug-related**

Adverse events – country results

Country	No. (%) of patients with AEs		No. (%) of patients with drug-related AEs	
	4-FDC	Single tablets	4-FDC	Single tablets
Egypt	10 (10.20)	8 (7.92)	5 (5.1)	6 (5.94)
India	12 (8.82)	14 (10.00)	6 (4.41)	13 (9.28)
Pakistan	25 (29.76)	27 (30.33)	23 (27.38)	24 (26.96)
Philippines	22 (23.15)	28 (29.47)	16 (16.84)	21 (22.10)
Thailand	60 (41.37)	40 (28.77)	55 (37.99)	30 (21.58)
Total	129	117	105	94



Discussion

Discussion

- This study is the **first adequately powered trial demonstrating the non-inferiority** of a WHO-compliant 4-FDC preparation in comparison to single tablets preparations in the treatment of sputum smear-positive pulmonary TB.
- The cure rates observed at EOT in the ITT population are in accordance with the cure rate of 82.2% reported at the end of a 6 months therapy in another well designed study using WHO outcome definitions, when considering all randomized patients (356/433).⁽¹⁾
- The high cure rates in the PP subgroup are comparable to the values of 93% to 99% reported by other authors when considering the bacteriologically documented cases of cure and failure only.⁽¹⁻⁴⁾

1- Jindani et al. Lancet 2004;364:1244-51

2- Kumaresan JA. et al. Int J Tuberc Lung Dis 1998;2:992-98

3- Lienhardt C. et al. Int J Tuberc Lung Dis 1998;2:712-18

4- Walley JD. et al. Lancet 2001;357:664-69

Discussion

- Although the WHO target of 85% success was not reached in the ITT at EOT (mainly because of drop outs), our cure rates compare well with the **74.4%** rate of successful outcomes reported in a recent European review.⁽⁵⁾
- Despite lower doses administered in the 4-FDC group (except R), equivalent overall efficacy was demonstrated throughout all study endpoints.
- It is unlikely that our follow-up period of 6 months may have significantly underestimated the true difference in relapse rates, since most recurrences have been reported to occur in the first 6 months post therapy.⁽⁶⁾

5- Faustini A. et al. Eur Respir J 2005 ;26 :503-10

6- Lambert ML et al. Lancet Inf Dis 2003;3;282-87

Discussion

- Although more drug-related AEs were reported in total in the 4-FDC group, the **overall safety profile** was in accordance with the **expected** undesirable effects of the antituberculosis agents used in this study.
- The trend towards a **lower incidence of gastrointestinal AEs** and the observation of significantly **less liver disorders** in the 4-FDC group fit well with the lower doses actually administered with the 4-FDC preparation.

Discussion

- Since the study was not blinded an increased safety awareness of the investigators could have led to a **tendency of over-reporting drug relatedness for some AEs observed in the 4-FDC group.** Although this interpretation has to be considered with caution, it would be in accordance with the fact that the overall number of patients with AEs (drug-related or not) was not significantly higher in the 4-FDC group, and that patients' overall assessment of tolerance showed the 4-FDC regimen to be significantly better tolerated.
- The present study demonstrated the equivalent overall efficacy of the 4-FDC regimen with a significantly improved patient acceptability, in comparison to single tablets regimen, and therefore supports the **WHO recommendations for 4-FDC therapy of smear positive pulmonary TB.**