Gemifloxacin Cutaneous Manifestations

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Understanding “The Rash”

- Epidemiology
  - Types
  - Incidence
    - Rash co-variants
  - Severity
- Pathophysiology
  - Study 344
- Risk Assessment
  - Cross and sub-clinical sensitization
  - Potential for cutaneous conditions of concern

Clinical Data Sources

- Clinical trial data
- Study 344
- Phase IV FORCE Study
- Phase IV Prescribing Use Study
- Post-marketing data

Rash Incidence

Duration of Therapy Important Co-Variant

	Clinical Trials			
	5-Day ABS Gemifloxacin 320 mg PO N=1,122 n (%)	7-Day ABS Gemifloxacin 320 mg PO N=724 n (%)	Gemifloxacin 320 mg PO N=8,119 n (%)	All Comparators N=5,248 n (%)
Rash*	29 (2.6)	62 (8.6)	283 (3.5)	59 (1.1)
SAE of rash*	1 (0.1)	3 (0.4)	7 (0.1)	1 (<0.1)
Rash* leading to withdrawal	3 (0.3)	17 (2.3)	62 (3.4)	15 (0.3)

* Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.

Rash Incidence

Duration of Therapy Greater Impact Than Age

	Clinical Trials		
Age Category	ABS 5-Day N=1,122 %	ABS 7-Day N=724 %	Overall Gemifloxacin N=8,119 %
<40 years	2.3	10.4	7.8
≥40 years	2.9	6.2	3.3

Rash Incidence

Duration of Therapy Greater Impact Than Gender

		Clinical Trials		
Gender	Age Category	ABS 5-Day N=1,122 %	ABS 7-Day N=724 %	Overall Gemifloxacin N=8,119 %
Female	Total	3.4	10.3	4.6
	<40 years	2.5	12.9	7.8
	≥40 years	4.4	7.3	3.3
Male	Total	1.3	6.2	2.3
	<40 years	1.8	7.3	4.2
	≥40 years	0.9	4.7	1.6

Rash Incidence
Duration of Therapy Most Important Co-Variant

	FORCE Study			
	AEBCB	CAP	All Indications	
Statistic	Gemifloxacin 5-Day N=1,408 n (%)	Gemifloxacin 7-Day N=413 n (%)	Gemifloxacin N=1,821 n (%)	Combined Controls N=900 n (%)
Patients with rash*	18 (1.3)	15 (3.6)	33 (1.8)	5 (0.6)
SAE of rash	0	0	0	0
Rash leading to withdrawal	4 (0.3)	1 (0.2)	5 (0.3)	3 (0.3)

* Rash includes combined terms of MedDRA 7.1 PTs rash, rash generalized, maculopapular rash, urticaria.

Rash Incidence

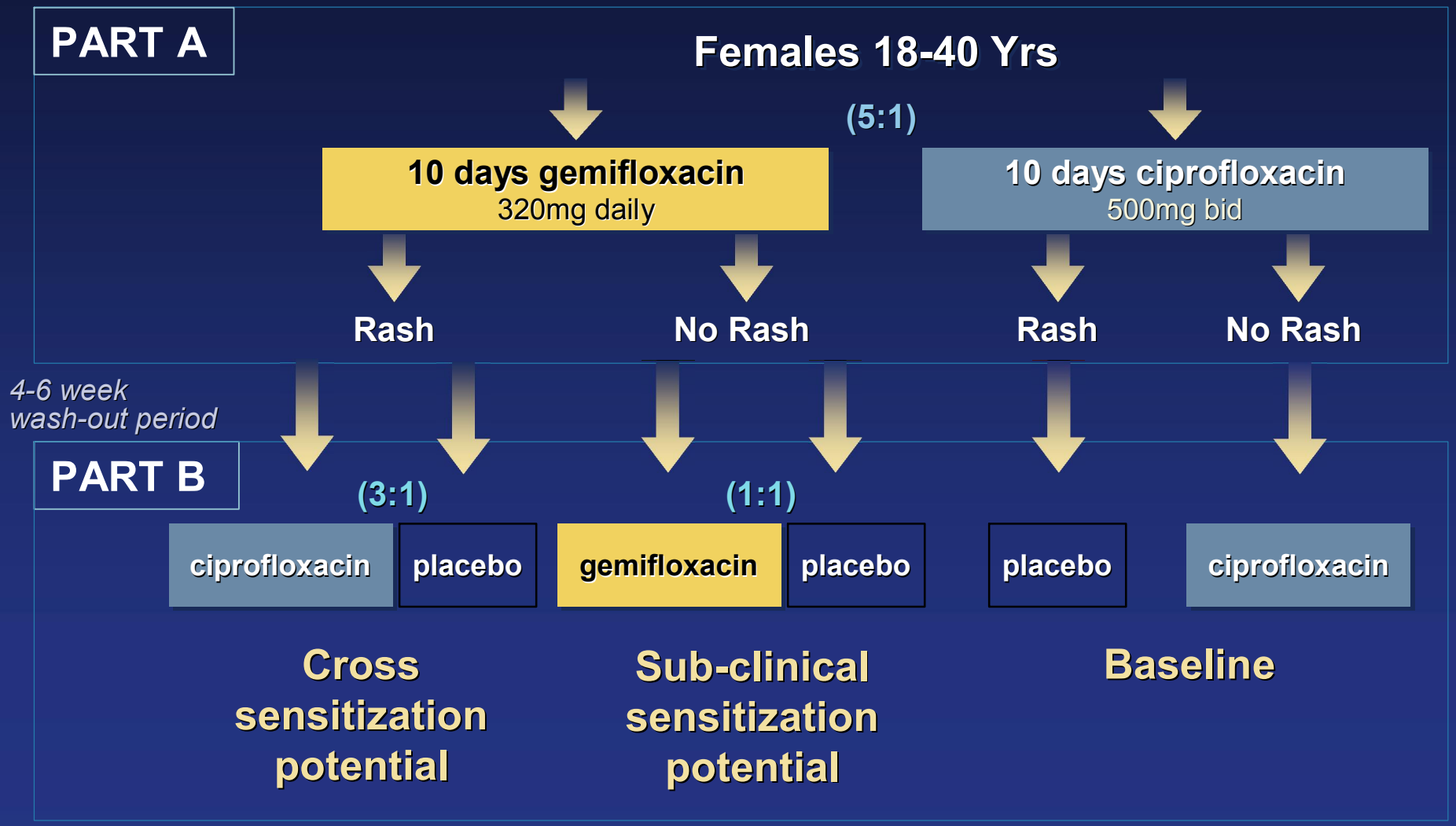
Rash Co-Variants Consistent With Clinical Trials

Gender		FORCE Study			
		AEBCB		CAP	
		Gemifloxacin N=1,408 %	Amoxicillin/ clavulanate N=686 %	Gemifloxacin N=413 %	Clarithromycin XL N=214 %
Female	Total	1.8	0.5	6.0	1.5
	<40 years	2.8	1.0	8.0	0
	≥40 years	1.5	0.3	5.0	2.0
Male	Total	0.5	0.4	0.6	0
	<40 years	0	0	2.0	0
	≥40 years	0.6	0.4	0	0

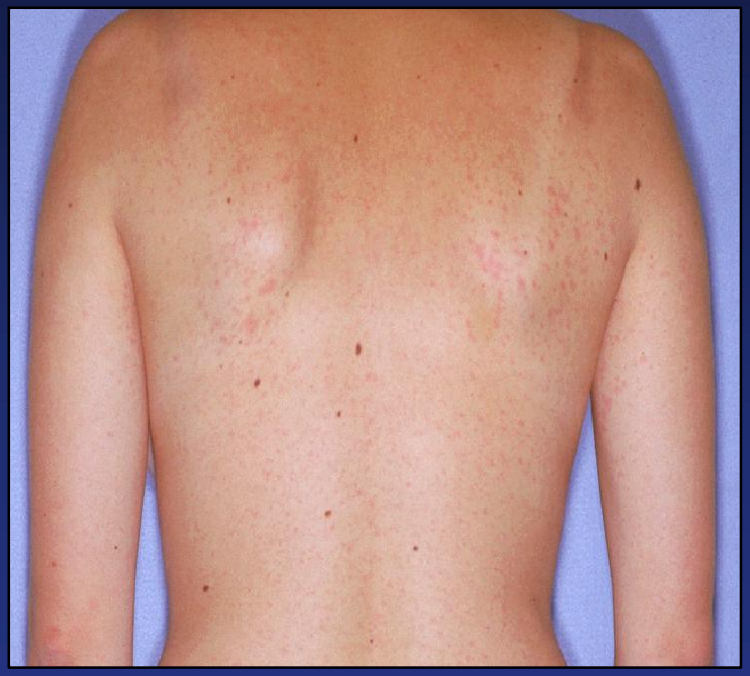
Objectives for Study 344
Dermatology Safety Study

- To assess rash (appearance, systemic, histology, severity)
  - By maximizing the rate of occurrence of rash
  - With extended dosing in an enriched population
- To understand cross sensitization potential
  - By treating subjects who had a gemifloxacin rash with ciprofloxacin
- To determine sub-clinical sensitization potential
  - By treating subjects with 2 consecutive prolonged courses of gemifloxacin

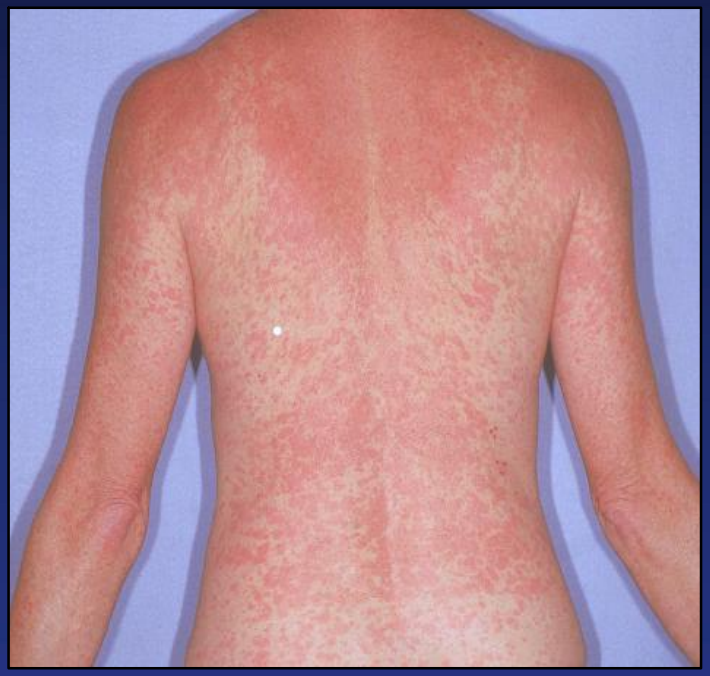
Study 344 Design



Study 344
Rash Morphology



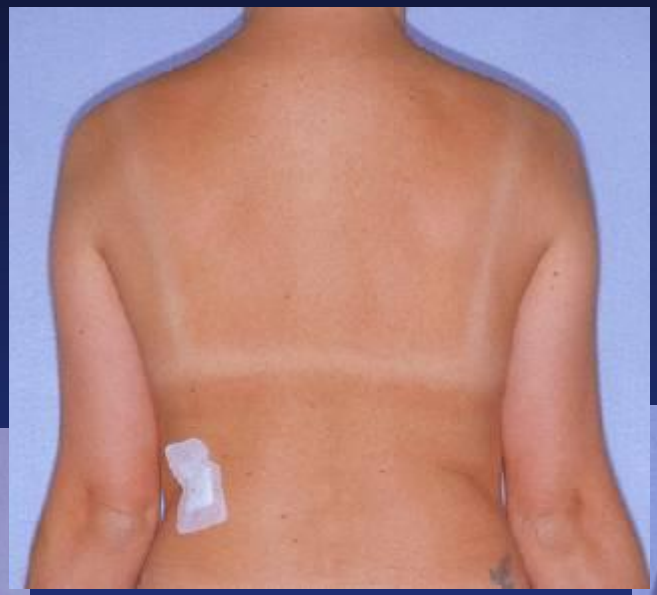
Average

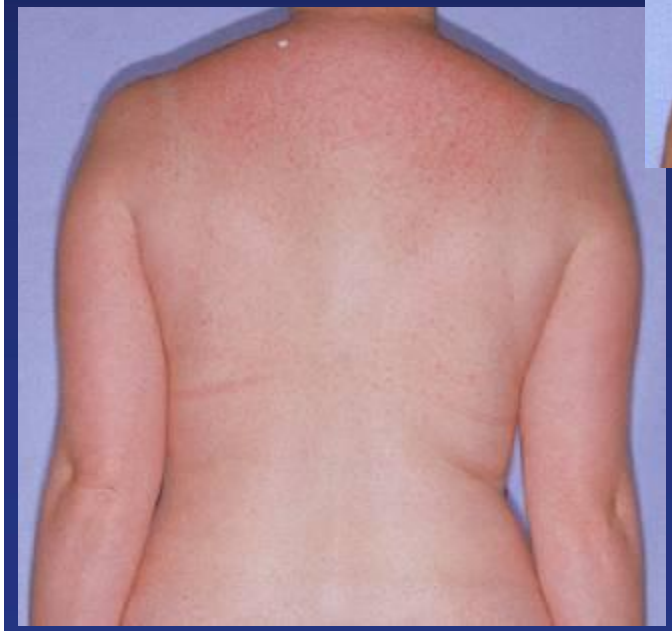


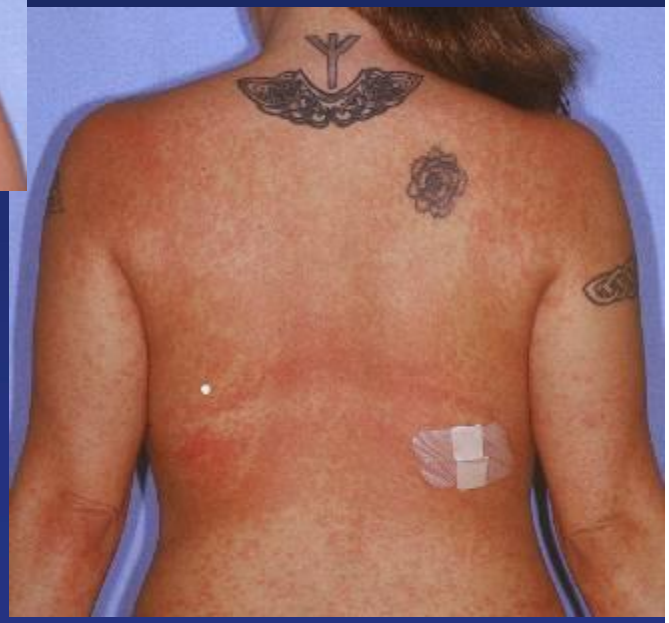
Worst

Study 344

What Investigators Reported as "Severe"







Study 344

Pathology Consistent with Mild Exanthematous Eruption

- Mild superficial perivascular lymphocytic infiltrate
- 10 biopsies showed a denser infiltrate
- Inflammatory infiltrate composed of lymphocytes
- Mixed CD4 and CD8 population
- No “interface” lymphocytic infiltrate
- No epidermal necrosis
- No vasculitis

Study 344
Low Cross Sensitization Potential

PART A

Females 18-40 Yrs

10 days gemifloxacin
320mg daily

Rash

4-6 week wash-out period

PART B

(3:1)

ciprofloxacin	**placebo**
# with rash	*8*	*1*
% with rash	*5.9%*	*3.5%*

Study 344
No Sub-Clinical Sensitization Potential

PART A

Females 18-40 Yrs

10 days gemifloxacin
320mg daily

No Rash

4-6 week wash-out period

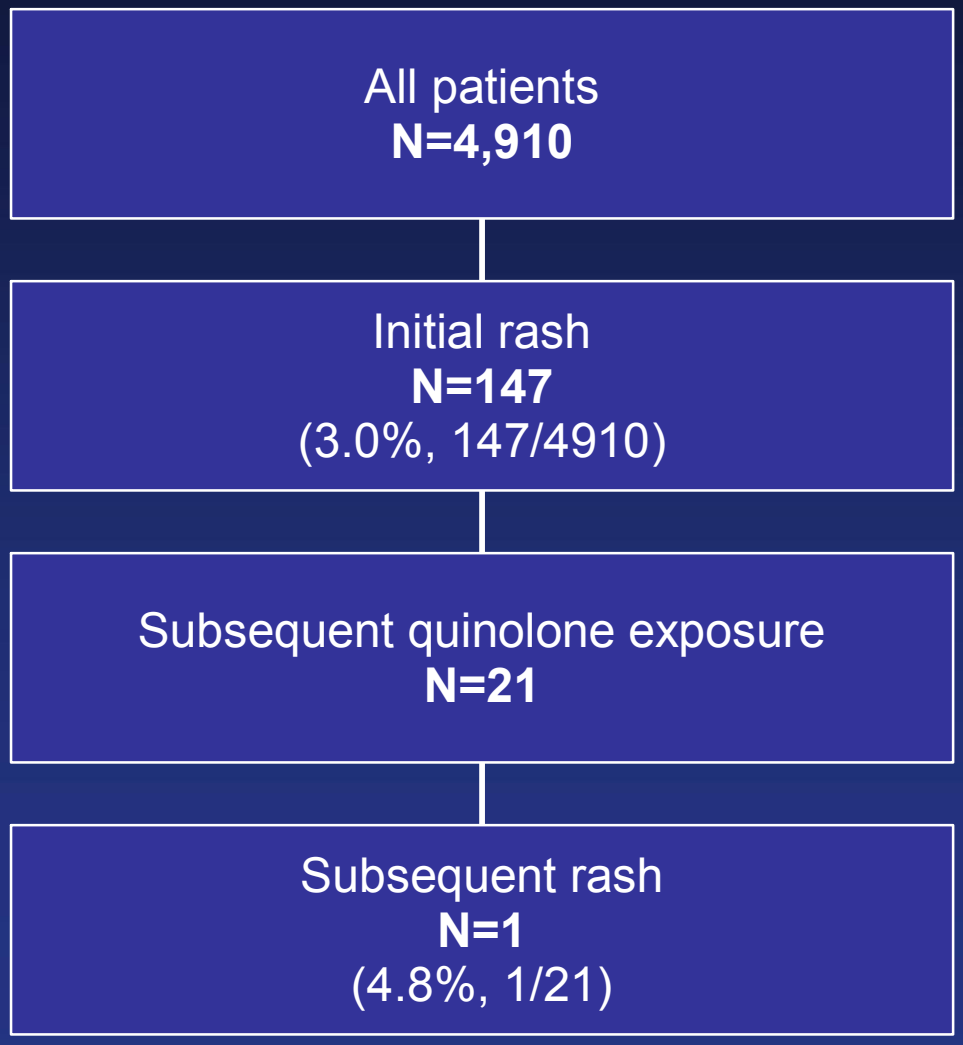
PART B

(1:1)

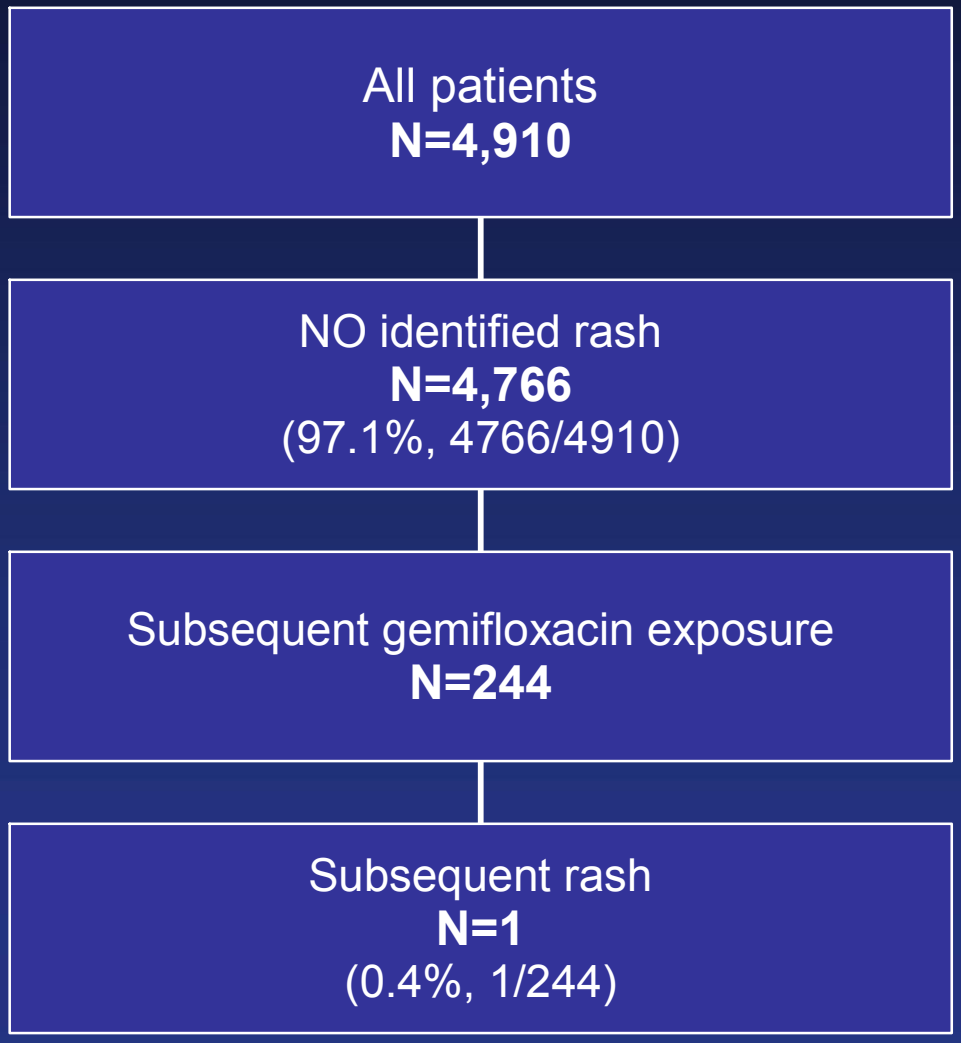
	gemifloxacin	**placebo**
# with rash	*6*	*5*
% with rash	*2.4%*	*2.0%*

Gemifloxacin Prescribing Use Study

Cross Sensitization Analysis



Gemifloxacin Prescribing Use Study
Sub-Clinical Sensitization Analysis



Evaluating Cutaneous Manifestations
Database Analysis

- Serious Adverse Events (SAEs)
- Morphology
- Fever (if any)
- Other organ involvement (if any)
- Eosinophilia

Rash SAEs
Rare in Gemifloxacin Trials

- Clinical trial population
  *N=7 out of 8,119 (**0.1%** overall)*
  - All 7 were exanthems
  - 1 was associated with mycoplasma
  - 1 was associated with mononucleosis
  - No systemic associations with skin reactions (mycoplasma subject had arthralgia)
- Study 344 - 0 rash SAEs / 819 patients
- FORCE Trial – 0 rash SAEs / 1,821 patients

Rash Intensity
Mostly Mild to Moderate

	Clinical Trials			
	5-Day ABS Gemifloxacin 320 mg PO N=1,122 n (%)	7-Day ABS Gemifloxacin 320 mg PO N=724 n (%)	Gemifloxacin 320 mg PO N=8,119 n (%)	All Comparators N=5,248 n (%)
Patients with AE of Rash*	29 (2.6)	62 (8.6)	283 (3.5)	59 (1.1)
Mild	14 (1.2)	24 (3.3)	138 (1.7)	33 (0.6)
Moderate	13 (1.2)	22 (3.0)	107 (1.3)	22 (0.4)
Severe	2 (0.2)	16 (2.2)	38 (0.5)	4 (0.1)

* Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.

Rash & Systemic Involvement
No Apparent Association

- Clinical trials
  - 39/8119 (0.48%) met eosinophilia, liver enzyme elevation criteria
    - 2/39 (5.1%) developed rash
  - 4 case of fever and rash
  - 1 with lymphadenopathy and rash
- Study 344
  - No association of rash with eosinophilia, liver involvement
  - 6 cases of fever, 1 with lymphadenopathy
- No Hypersensitivity Syndrome

Clinical trials, 344, FORCE
Significant Cutaneous Manifestations

- 1 angioedema
- No Hypersensitivity Syndrome reaction
- No SJS/TEN

Post-Marketing Surveillance (AERS)
A Review of 760,000 U.S. Patients

- All MedWatch cutaneous reports reviewed
- Same structured methodology as used to analyze clinical trials
  - Serious Adverse Events (SAEs)
  - Morphology
  - Fever (if any)
  - Other organ involvement (if any)
  - Eosinophilia

Post-Marketing Surveillance (AERS)
A Review of 760,000 U.S. Patients

- FDA identified other criteria
  - Serious allergic reactions with skin manifestations
  - Erythema multiforme
  - Skin exfoliation

MedWatch Rash Reports

- 706 reports
- 31 SAEs
  - 3 possible cases of SJS
- 24 other cutaneous cases of concern

AERS Database
Details of Serious Adverse Events (Skin)

- 14 simple exanthems
- 1 urticaria
- 1 photosensitivity
- 6 exanthems with fever
- 3 Stevens Johnson Syndrome
- 2 angioedema
- 2 anaphylaxis
- 1 vasculitis (no biopsy)
- 1 hemophagocytic syndrome

Reports of Rashes of Potential Concern

- 7 other cases of fever in association with rash
- 6 cases of arthralgia / arthritis / joint swelling
- 1 case of liver enzyme elevation
- 1 case of eosinophilia
- 3 cases of skin exfoliation
- 3 cases of mucosal involvement
- 3 cases of erythema multiforme

Case 1: 2004USFACT00083
Stevens Johnson Syndrome

- 67-year old female
- Rash appeared on day 3 or 4 of treatment
- Patient hospitalized for 2-3 days
- Neither fever nor systemic symptoms reported

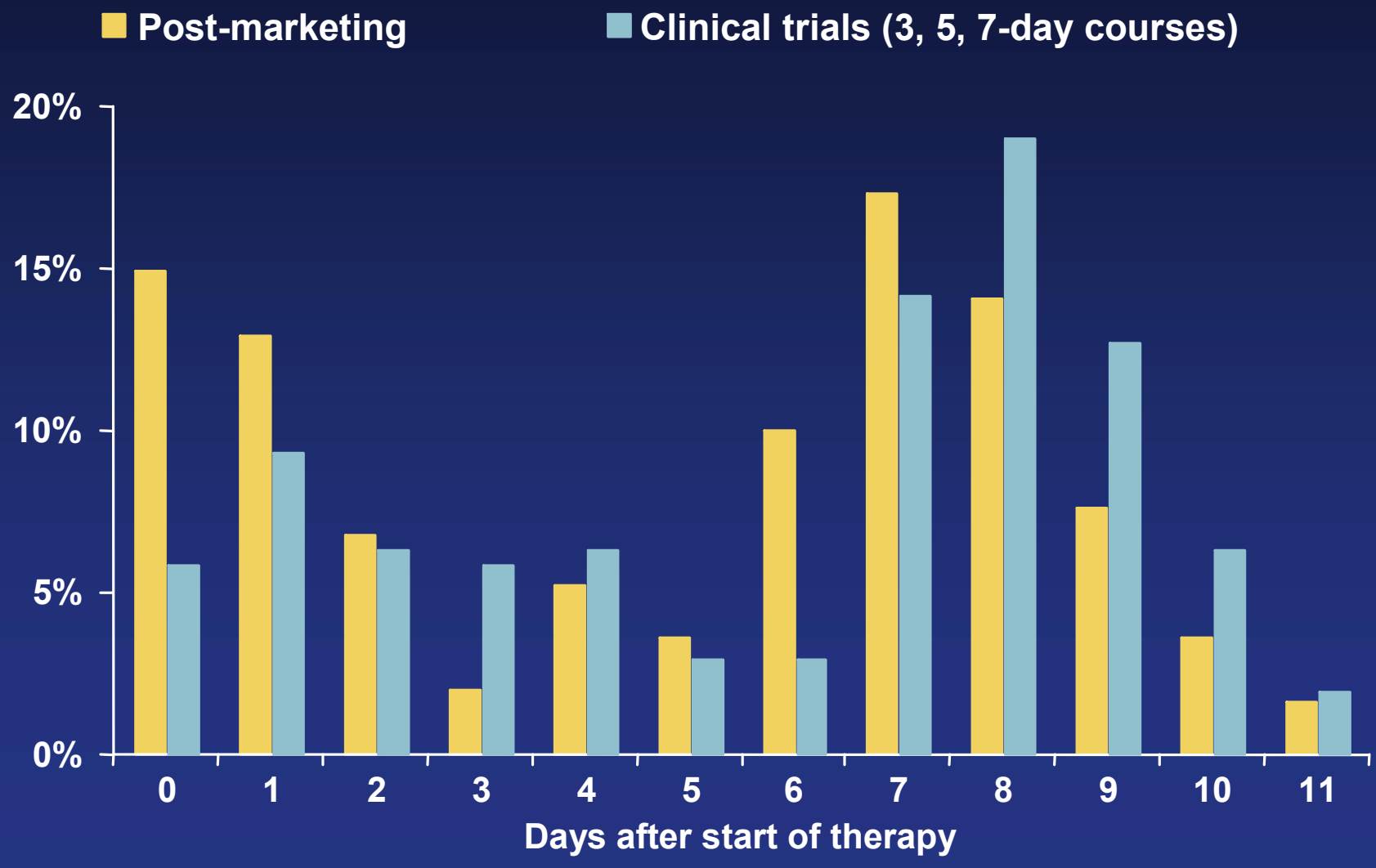
Case 2: FACT0600069
Stevens Johnson Syndrome

- 18-year old female
- Prescribed gemifloxacin for “strep throat”
- Developed itchiness after 1 dose later described as hives
- Hospitalized with discolored skin, blisters in mouth and vagina
- SJS not “medically confirmed”
- No cutaneous blistering reported
- Treated with steroids and discharged after 7 days

Case 3: 2005USFACT00342
Stevens Johnson Syndrome

- Patient developed severe rash after starting drug
- Dose, duration, condition, medical history, gender, age not reported
- Physician reported rash as “not maculopapular, not benign” and “like SJS”
- Patient admitted to hospital, treated with epinephrine and other meds (not described)

Time to Onset of Rash



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Gemifloxacin Rash Safety Profile

Consistent Data: All Studies , Post-Marketing Experience

- Mostly mild-to-moderate exanthematous rash
- Possible cutaneous conditions of concern
  - SSLR – no cases
  - Hypersensitivity Syndrome – no cases
  - SJS – 2 possible cases
  - TEN – no cases
- Low cross sensitivity
- No sub-clinical sensitivity