The SOLITAIRE-Oral Trial:

Results from a Phase 3 Trial in Moderate to Moderately Severe Community-Acquired Bacterial Pneumonia (CABP) Treated as Outpatients with a New Oral Macrolide, Solithromycin

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The presenter, Dr. Carlos Barrera, received research funding for the conduct of the study, but has no other financial conflict of interest to report.

Drs. Rowe, Nitu, Mykietiuk, Metev, Laabs, Mitha, Tanaseanu, McDermott Molina, Antonovsky, Van Rensburg, Flores, Sokolowska and Doreski, all study investigators, received research funding for the conduct of the study

Dr. Anita Das, the study statistician, is a consultant to Cempra

K Clark, B Jamieson, A Sheets, K Keedy, P Fernandes, & D Oldach are all employees of Cempra, and Cempra stock holders.

Topics

Introduction

Solithromycin Background

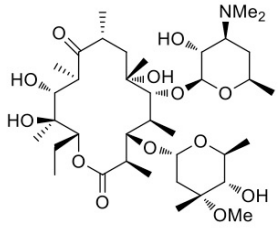
Study Design, SOLITAIRE-Oral

Study Results

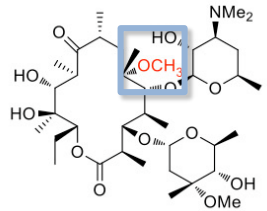
Conclusions

Currently Approved Macrolides

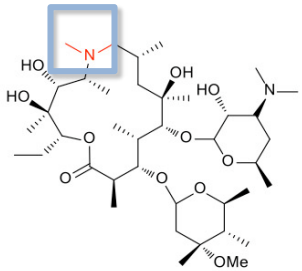
ERYTHROMYCIN



CLARITHROMYCIN



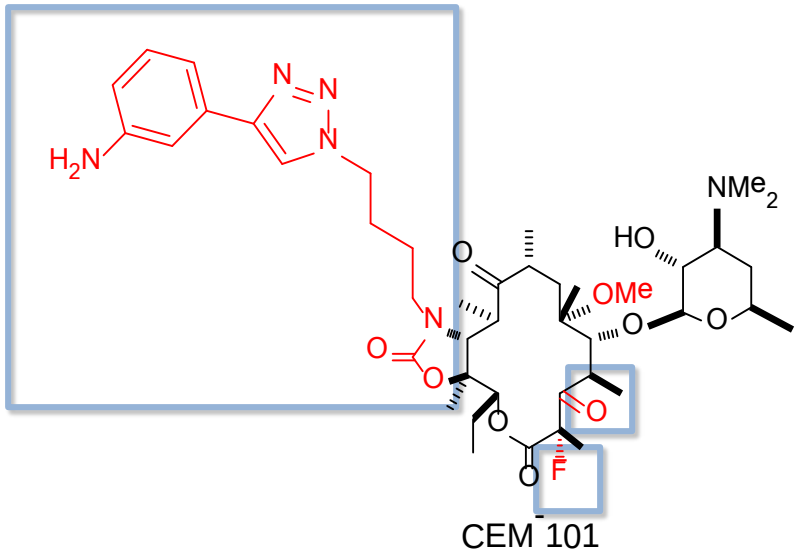
AZITHROMYCIN



Solithromycin:

4th Generation Macrolide, First Fluroketolide

SOLITHROMYCIN



CEM 101

= 3 Changes Made to Make Solithromycin

Interacts with Bacterial Ribosome at Three Sites – Resistance Rare and Could Only Occur If Mutations Occur at Three Distinct Sites

Solithromycin – Solitaire Phase 3 CABP Trials

SOLITAIRE

FORMULATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
1 Oral				
2 IV-to-Oral				

SOLITAIRE ORAL		SOLITAIRE IV-to-ORAL
• Blinded, Randomized 1:1, Global • Soli = 5 days; Avelox = 7 days	TRIAL DESIGN	• 2x Sites + More Countries than Oral • 7 Day IV: MD Determines Oral Switch
Avelox (Moxifloxacin)	COMPARATOR	Avelox (Moxifloxacin)
860	PATIENTS (n)	860
Non-Inferiority in ECR and SFU Success	PRIMARY ENDPOINT	Non-Inferiority in ECR and SFU Success
Microbial ITT; Safety	SECONDARY ENDPOINT	Microbial ITT; Safety
Completed Enrollment Q3 2014 Data Presented, ECMID 2015	STATUS	Currently Enrolling

Combined Data For NDA/MAA

Solitaire-Oral Phase 3 Trial: Objectives and Endpoints

Primary objective and endpoint (for FDA)

- Non-Inferiority (NI) in Early Clinical Response (ECR) rate in the ITT pop

  Improvement at 72 hours (-12/+36) in at least two of the following symptoms: chest pain, cough, difficulty with sputum production, and dyspnea… without worsening in any

Primary objective and endpoint (for EMA)

- NI in success rate at SFU (short term follow-up visit, 5 to 10 days after end of therapy)
  in the ITT and clinically-evaluable (CE) populations

  Success or failure as determined by the investigator

Secondary objectives

- NI in early clinical response rate at 72 (-12/+36) hours in the pooled mITT population from the two Phase 3 trials
- NI in early clinical response rate at 72 (-12/+36) hours in the individual study mITT population
- Safety and tolerability of oral solithromycin vs oral moxifloxacin

Solitaire-Oral Phase 3 CABP Study Outline

860 CABP Patients, Oral Solithromycin vs Oral Moxifloxacin

1:1 Randomization

- Stratified by geographic region, by history of asthma and/or COPD, and by PORT* score (II vs III/IV)
- PORT II severity pneumonia capped at 50%. PORT IV enrollment limited to PSI Score < 105

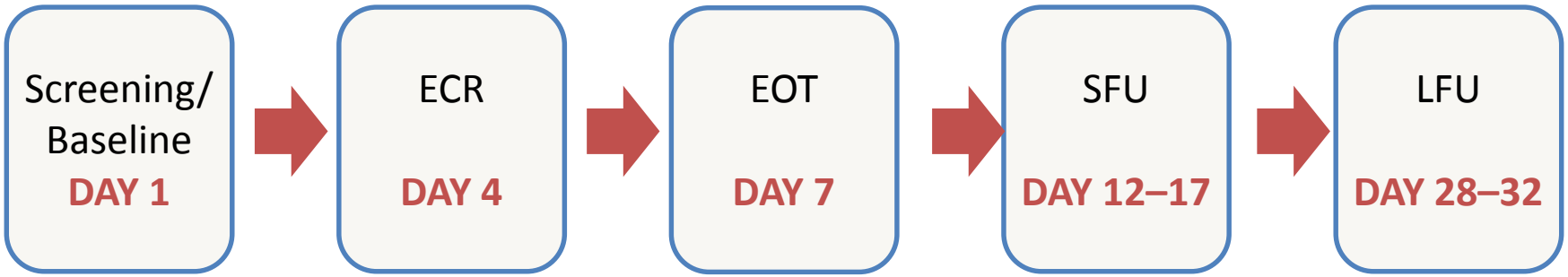
Enrollment Criteria

- Acute onset or worsening of at least 3 of 4 cardinal symptoms: cough, dyspnea, chest pain, and sputum production
- Must have fever, hypothermia and/or physical examination findings of CABP
- Chest radiograph with lobar or patchy parenchymal pulmonary infiltrates
- Not hospital or health care associated; no long-acting antibiotic during prior 7 days

Treatment

- Solithromycin: 5 days therapy (800 mg on day-1, 400 mg days 2–5, placebo on days 6–7)
- Moxifloxacin: 7 days therapy (400 mg on days 1–7)

Solitaire-Oral Visit Schedule



Study Drug Dosing **DAYS 1 to 7**

ECR= Early Clinical Response…time point for primary endpoint assessment for FDA

SFU= Short-Term Follow-up Visit (also known as 'Test of Cure' visit)…time point for primary endpoint assessment for EMA

LFU= Long-Term Follow-up Visit

Solitaire-Oral Phase 3 CABP Trial: Study Populations

	SOLITHROMYCIN	MOXIFLOXACIN
Intent to Treat Population [ITT] N	426	434
Safety (%)	424 (99.5)	432 (99.5)
Microbiological ITT Population [mITT] (%)	235 (55.2)	226 (52.1)
Clinically Evaluable at SFU [CE-SFU] (%)	388 (91.1)	390 (89.9)
Microbiologically Evaluable at SFU [ME-SFU] (%)	220 (51.6)	211 (48.6)

Solitaire-Oral Phase 3 Trial: Baseline Characteristics and Enrolling Geographical Regions/Countries

	Solithromycin	Moxifloxacin
Mean Age (years)	58.5	56.7
% ≥ 65 years of age	36.4%	31.6%
Male gender (%)	53.3%	52.8%
h/o asthma or COPD	14.6%	14.7%
PORT I*	1* (0.2%)	0
PORT II	209 (49.1%)	223 (51.4%)
PORT III	168 (39.4%)	173 (39.9%)
PORT IV	48 (11.3%)	38 (8.8%)

Enrollment by Regions/Countries
North America 23.7%, Europe 52.1%,
Latin America 12.3%, South Africa 11.9%

Solitaire-Oral: mITT Population Baseline Pathogens

Pathogen	SOLITHROMYCIN N=235 (55.2% of ITT)	MOXIFLOXACIN N=226 (52.1% of ITT)
Staphylococcus aureus	22 (9.4%)	14 (6.2%)
Any *Streptococcus pneumoniae*:	95 (40.4%)	102 (45.1%)
Urine Antigen positive	15 (6.4%)	13 (5.8%)
Bacteremia	5 (2.1%)	10 (4.4%)
Positive Blood or Respiratory Specimen	83 (35.3%)	95 (42.0%)
Macrolide resistant Spn	11 (4.7%)	8 (3.5%)
β-hemolytic streptococci (Groups A, B, or C)	3 (1.3%)	4 (1.8%)
Hemophilus influenzae	80 (34.0%)	55 (24.3%)
Moraxella catarrhalis	28(11.9%)	23 (10.2%)
Hemophilus parainfluenzae	6 (2.6%)	5 (2.2%)
Klebsiella pneumoniae	7 (3.0%)	5 (2.2%)
Mycoplasma pneumoniae	37 (15.7%)	42 (18.6%)
Mycoplasma by culture or PCR (not serol.)	21 (8.9%)	28 (12.4%)
Legionella species (includes 1 *L. dumoffii*)	61 (26.0%)	64 (28.3%)
Legionella by UAT or Culture (not serol.)	7 (3.0%)	3 (1.3%)

Solitaire-Oral Phase 3 Trial: Early Clinical Response (ECR) in ITT Populations (and Subgroups)

Population	SOLITHROMYCIN Success Rate %	MOXIFLOXACIN Success Rate %	Difference	95% CI
ECR-ITT	78.2 (333/426)	77.9 (338/434)	0.29 %	(-5.5, 6.1)
ECR-PORT I/II	80.5 (169/210)	80.7 (180/223)	-0.24 %	(-8.2, 7.7)
ECR-PORT III/IV	75.9 (164/216)	74.9 (158/211)	1.04 %	(-7.6, 9.7)
ECR- Age < 65	77.9 (211/271)	80.8 (240/297)	-2.95 %	(-10.0, 4.1)
ECR- Age 65–74	75.3 (70/93)	73.0 (54/74)	2.30 %	(-12.3, 16.9)
ECR- Age ≥ 75	83.9 (52/62)	69.8 (44/63)	14.03 %	(-2.1, 30.2)
Hx of COPD or Asthma	71.0 (44/62)	67.2 (43/64)	3.78	(-13.9, 21.5)

Solitaire-Oral Phase 3 Trial: Success at SFU in the ITT and CE Populations (and Subgroups)

Population	SOLITHROMYCIN Success Rate %	MOXIFLOXACIN Success Rate %	Difference	95% CI
SFU-ITT	84.5 (360/426)	86.6 (376/434)	-2.13%	(-7.1, 2.8)
SFU-ITT PORT II	86.2 (181/210)	89.2 (199/223)	-3.05%	(-9.7, 3.6)
SFU-ITT PORT III/IV	82.9 (179/216)	83.9 (177/211)	-1.02%	(-8.5, 6.5)
SFU-ITT: Hx of COPD/Asthma	91.9 (57/62)	85.9 (55/64)	+6.0 %	(-6.5, 18.5)
SFU-CE	88.1 (342/388)	91.3 356/390	-3.14%	(-7.7, 1.4)
SFU-CE PORT II	89.3 (175/196)	92.1 (187/203)	-2.83%	(-9.0, 3.4)
SFU-CE PORT III/IV	87.0 (167/192)	90.4 (169/187)	-3.40%	(-10.3, 3.5)
SFU-CE: Hx of COPD/Asthma	93.2 (55/59)	89.8 (53/59)	+3.39	(-8.3, 15.1)

Streptococcus pneumoniae

Leading diagnosis, globally (diagnosed in 23% of study subjects)

Multiple Diagnostic Methods Utilized:

Blood Culture +
Sputum Cx +
Sputum PCR +
Urine Antigen Test +
Nasopharyngeal Swab Q-PCR +

Overall Early Clinical Response in 76% (vs. 83.3% with moxifloxacin)

- **In patients with bacteremia: 60% (vs. 70% with moxifloxacin)**

Overall Short Term Follow-Up Response in 84.4% (versus 87.3% with moxifloxacin)

- **In patients with bacteremia: 60% in both treatment arms**

Solitaire-Oral Phase 3 Trial: Safety Outcomes

	SOLITHROMYCIN 800/400 mg QD (N=424)	MOXIFLOXACIN 400 mg QD (N=432)
Any Treatment-Emergent Adverse Event (TEAE)	155 (36.6%)	154 (35.6%)
Any Study Drug Related TEAE	43 (10.1%)	54 (12.5%)
Any Serious Adverse Event (SAE)	28 (6.6%)	27 (6.3%)
Premature Discontinuation of Study Drug from Adverse Events	16 (3.8%)	13 (3.0%)
Deaths	6 (1.4%)	6 (1.4%)

- ✓ Solithromycin Demonstrated an Acceptable Safety and Tolerability Profile, Comparable to Moxifloxacin
- ✓ No SAEs attributed to Solithromycin

Solitaire-Oral: Treatment Emergent Adverse Events

	SOLITHROMYCIN (N=424)	MOXIFLOXACIN (N=432)
Headache	4.5%	2.5%
Diarrhea	4.2%	6.5%*
Nausea	3.5%	3.9%
Emesis	2.4%	2.3%
Dizziness	2.1%	1.6%
ALTs** - Grade 3	4.6%	2.1%
Grade 4	0.5%	1.2%

No patient reported accommodation disorder (visual disturbance)

* 2 patients with *C. difficile* associated diarrhea were identified, both received moxifloxacin

** No patient in either arm of the study developed treatment emergent elevation of both ALT and bilirubin meeting Hy's Law criteria. Observed ALT elevations were reversible and asymptomatic.

Solitaire-Oral Phase 3 CABP Trial

TAKE AWAY POINTS

Oral Solithromycin Monotherapy Is Non-inferior to Oral Moxifloxacin for Treatment of Moderate- to Moderately-Severe (PORT II-IVa) CABP

- Efficacy was comparable and the mortality rate was identical between the two treatment arms. Overall mortality (1.4%) was lower than predicted based on PORT score distribution
- A microbiological diagnosis was established in > 50% of patients. Efficacy across pathogens was comparable between the two treatment arms
- Safety comparable, more Grade 4 ALT events and all *C. difficile* infections observed in the moxifloxacin arm
- Solithromycin showed greatest ECR efficacy in the elderly, the most at-risk population for CABP