POSTER# 93 OR

REAL-WORLD EXPERIENCE WITH SINGLE- AND MULTI-DOSE ORITAVANCIN

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ABSTRACT

Background: Oritavancin (ORI) is indicated for the treatment of adult patients with ABSSSI as a single 1200-mg parenteral dose. Therapies that can avoid daily parenteral injections may facilitate a reduction in patient visits, healthcare resources, and IV line complications.

Methods: The second phase of a non-interventional retrospective registry (CHROME II) enrolled 328 patients from 21 U.S. sites who were administered ≥ 1 dose of ORI.

Results: The average patient age was 57yo and 36% were ≥ 65yo. Median weight and BMI were 92 kg and 31 kg/m^2, respectively, with hypertension (56%), diabetes (40%), hyperlipidemia (33%), and PVD (17%) as the most frequent co-morbidities. Prior antibiotic therapy was observed in 72% of patients with 49 separate regimens, most containing vancomycin; 18% of patients received non-ORI agents following the last or single dose of ORI. Skin and soft tissues accounted for 93% of infections. *S. aureus* was cultured from 73% of infected sites with equal proportions of MSSA and MRSA.

In a real-world registry oritavancin was administered to treat a variety of deep-seated and complicated infections. Fifty-one patients (16%) treated at 15 sites received multiple ORI doses (range, 2-10), primarily for SSTIs (84%); 31 and 11 patients received ≥ 2 or ≥ 3 doses ORI 1200mg doses at intervals of ≤ 14d, respectively, primarily for SSTIs (43/51). Of the 11 patients, 10 were medically evaluable; clinical response occurred in 90% of these patients.

Overall, clinical response was noted in 77% of ORI-treated patients. For patients receiving ≥ 3 ORI doses clinical response was 92%. TEAEs were reported in 5.8% and 15.7% of patients who received single or multiple doses of ORI, respectively. SAE or severe AEs were reported in 2 patients. No cases of CDAD or osteomyelitis were reported.

Conclusion: Several recent patient cases and case series describe the use of ORI in multiple-dose regimens for the treatment of deep-seated infections, including bone and joint infections, pneumonia, bacteremia, and complicated surgical site infections. We described the first multi-center non-interventional real-world experience in patients prescribed ORI, including multiple dose regimens.

INTRODUCTION

- **Registrational trials of antibiotics for ABSSSI.** In an effort to eliminate ambiguity of clinical definitions and to provide objective criteria that can be evaluated statistically, the FDA incorporated into clinical trials well-defined reliable and reproducible markers of early resolution of SSTIs and excluded patients with underlying diseases, confounding medications, or severe infection, such as necrotizing fasciitis, joint infection, gas gangrene, and osteomyelitis [1].
- **Phase 3 clinical trial with ORI.** Two identical phase 3, international, randomized, and double-blind trials (SOLO I and SOLO II) demonstrated that a single 1200-mg intravenous (IV) dose of ORI was noninferior to vancomycin at a dose of 1 g or 15 mg/kg every 12 hours for 7 to 10 days for the treatment of ABSSSI [2-4].
- **Registrational trials of antibiotics for ABSSSI.** In an effort to simplify management of SSTIs, the 2014 IDSA guidelines [5] addressed diagnosis and management according to severity of

INTRODUCTION (CONT'D)

- **Registrational trials of antibiotics for ABSSSI (cont'd).** of symptoms in both purulent or non-purulent infections (i.e., abscess and cellulitis), or in wound infections. The guidelines importantly address unclear management issues, such as recurrent abscesses, necrotizing fasciitis, pyomyositis, human/animal bite wounds, and SSTIs in immunocompromised patients. Unfortunately, in many regards, the lack of evidence-based approaches to management of many deep-seated SSTIs caused by endogenous pathogens makes way for better understanding clinical decisions made based on physicians' best opinion, or extrapolation from other patient populations.
- **CHROME Registry.** A patient registry for oritavancin (Clinical and Historic Registry and Orbactiv Medical Evaluation [CHROME]) was established in 2015 to characterize the use of ORI in post-marketing real-world settings. CHROME is a multicenter, multiyear, retrospective observational study to characterize the population of adult patients who have received ORI for the treatment of infections due to presumed or confirmed gram-positive bacteria and to describe the associated clinical and microbiologic outcomes and safety. We have presented results on the first 112 patients enrolled in the first phase of the CHROME registry [6]. The second phase extends the experience to additional patients as familiarity with ORI grows.
- **Clinical unmet needs in the treatment of SSTIs.** Post-marketing registries may narrow a knowledge gap by studying the use of antibiotics in real-world scenarios where the confluence of healthcare resources, patient preference, infection type, pathogen, and setting of follow-on therapy can dictate care decisions in unusual clinical situations. Furthermore, post-hoc analyses [7-8] provide additional data on the safe and effective use of ORI in specific subpopulations.

METHODS

- Sites (n=21,U.S. only) enrolled at least 10 consecutive patients who had received ≥ 1 ORI dose. To be enrolled, patients had to (1) be treated with ORI for a suspected or confirmed GP infection as monotherapy or part of a broader regimen and (2) have received the last dose of ORI at least 60 days prior to data entry into the electronic case report form (eCRF).
- Investigators were trained on the use of a standardized eCRF instrument. Sites utilized eClinicalOS (IBM Clinical Development; Durham, NC) as the data entry platform. Site audits were conducted remotely through a series of validation steps and data queries.
- Safety definitions were established by a Global Pharmacovigilance committee a priori. Safety data were collected up to 60 days following the last dose of ORI. Adverse events with a reasonable possibility of a causal relationship to ORI, as assessed by the Investigator, were reported and categorized based on their seriousness and severity.
- Clinical categories of efficacy assessed between end of infusion and 30 days followed standard definitions of cure, improvement, failure, or non-evaluable. Microbiologic response included eradication, presumed eradication, persistence, or non-evaluable.
- Results were descriptive, and no statistical analysis was performed on the data presented herein.

RESULTS

- Key baseline patient characteristics are provided in **Table 1**.

TABLE 1. PATIENT CHARACTERISTICS AND DEMOGRAPHICS

Characteristic	Value	Characteristic	Value
Age (yrs)		WBC>12,000 cells/mm^3 (%)	14.1
Median	57.5	Co-morbidities, %	
Range	18-98	Hypertension	56.4
≥ 65 yrs	36.3	Diabetes mellitus	40.2
Male (%)	53	Diabetic neuropathy	16.2
Race, white (%)	93.4	Diabetic foot infection	11.3
BMI (kg/m2)		Hyperlipidemia	33.5
Median	31.4	Vascular disease	16.8
Range	14-64	Dialysis (no.)	3
SIRS, at presentation (%)	10.0	SOT (no.)	9
Serum creatinine (mg/dL)		Prosthetic device, no. (%)	50 (15.2)
Mean (SD)	1.00 (0.47)	Single dose ORI (no.)	41
Range	0.3-4.7	> 1 dose ORI (no.)	9
		Current IVDA, no. (%)	23 (7.0)

- Infection types are provided in **Table 2** for 328 patients enrolled.

TABLE 2. INFECTION CLASSIFICATION (N=328)

Infection Classification	No. Patients (%)
Skin and skin structure	305 (93.0)
Cellulitis, non-purulent	157 (51.5)
Cellulitis, purulent	34 (11.1)
Wound	51 (16.7)
Surgical	21 (41.2)
Traumatic	12 (23.5)
Other	18 (35.3)
Abscess	35 (11.5)
Single	25 (71.4)
Multiple	10 (28.6)
Other SSTI	28 (9.1)
Bacteremia	7 (2.1)
Primary	5
Secondary to SSTI	2
Other	16 (4.9)
Osteomyelitis	7
Prosthetic joint infection	4
Septic arthritis/synovitis (native)	3
Endocarditis, native valve	1
Catheter exit site	1

- Overall, 29.3% (96/328) of patients had a confirmed microbiologic culture. The presence of *S. aureus* was common (72.9% of positive cultures) and exactly half were attributable to MRSA and MSSA. Only 8 GN isolates were observed as mixed infections. The remaining bacterial isolates were unidentified staphylococci and streptococci.
- In the 30 d prior to the first dose of ORI, 71.6% of patients received 49 unique antibiotic combinations of a non-ORI systemic antimicrobial. Vancomycin was the most common single agent used in the pre-ORI period (49.4% of patients). In patients receiving > 1 dose of ORI, only 9 of 51 patients received a systemic antibiotic between the first and last dose of ORI. After the last dose of ORI, 56 patients (17.1%) received a systemic antibiotic.

RESULTS (CONT'D)

- Of 328 patients, 51 (15.5%) received 2 to 10 doses of ORI. Single and multiple dose treatments are presented in **Table 3** according to infection type. Fifteen of 21 sites used multiple ORI doses to treat at least one patient.
- The following number of doses amongst 51 patients was distributed as follows: 2 doses (32), 3 doses (8), 4-6 doses (7) and ≥ 7 doses (4).
- Multiple dose regimens were differentiated according to the days of interruption between ORI doses. Empirically, interruption by 14 days or less was defined as an ORI treatment. This included 11 patients treated with at least 3 doses. Patients receiving multiple doses of ORI separated by >14 days were generally a result of recurring infection which is common with SSTIs.

TABLE 3. DOSING ACCORDING TO INFECTION CLASSIFICATION (N=328)

Major Primary Infection Classification	No. patients (%)
Skin and skin structure	305 (93.0)
Single	262 (85.9)
Multiple	43 (14.1)
Bacteremia	7 (2.1)
Single	7 (100)
Multiple	0
Other (not primary bacteremia)	16 (4.9)
Single	8 (50)
Multiple	8 (50)

- Clinical outcome is provided in **Table 4** for receipt of single dose ORI, 2 doses of ORI, and > 2 doses of ORI. Of 328 patients enrolled, clinical evaluation was performed on 226 patients. Overall, clinical response amongst all evaluable patients was 77.4%.

TABLE 4. CLINICAL OUTCOMES FOR EVALUABLE PATIENTS (N=226)

Outcome, % (n/N)	Single Dose	Two Doses	Three or More Doses
Clinical response	77.4 (151/195)	66.7 (12/18)	92.3 (12/13)
Clinical cure	50.3 (98/195)	38.9 (7/18)	46.2 (6/13)
Clinical improvement	27.2 (53/195)	27.8 (5/18)	46.2 (6/13)
Clinical failure	22.6 (44/195)	33.3 (6/18)	7.7 (1/13)

- Investigators reported treatment-emergent adverse events (TEAEs) considered as definitely or possibly related to ORI in 7.3% (24/328) of patients (**Table 5**). The most common TEAE (12/24) was pruritis. Discontinuation of ORI was observed in 6 patients and a single patient was reported to have serious adverse events which included asthenia, nausea and vomiting. Eight patients were not administered full doses (1200 mg) of ORI as a result of infusion-related adverse events. There were no deaths amongst enrolled patients.

TABLE 5. TREATMENT EMERGENT ADVERSE EVENTS IN THE SAFETY EVALUABLE POPULATION (n=328)

Category, % (n)	Single Dose (n=277)	Multiple Doses (n=51)
Any TEAE	5.8% (16)	15.7% (8)
TEAE leading to drug discontinuation	0.7% (2)	7.8% (4)
Serious AE	0.4% (1)	0
TEAE with fatal outcome	0	0

CONCLUSION

- **Multiple Dose Experience With ORI.** Several recent patient cases and case series describe the use of ORI in multiple-dose regimens for the treatment of deep-seated infections, including bone and joint infections, pneumonia, bacteremia, and complicated surgical site infections [9-11]. We described the first multi-center non-interventional real-world experience of ORI including regimens with more than a single dose.
- **Registry Experience in CHROME II.** Multiple doses of ORI to complete therapy of a deep-seated or otherwise complicated infection is an effective and safe alternative to daily infusions of shorter half-life antibiotics. Over time, familiarity with ORI has extended to its limited use by some clinicians as weekly or twice monthly infusions. In this registry, 11 patients received 3 to 10 doses of ORI 1200 mg over 3 hours as a single therapeutic course against surgical and non-surgical complicated wounds, including osteomyelitis. Clinical cure or improvement was observed in 9 of 10 evaluable patients in this cohort, with a single patient experiencing mild nausea.
- **Additional Studies.** The results of CHROME, both on-label and off-label uses of ORI, should be verified in larger multicenter open-label cohort studies with complicated and microbiologically documented infections. Multiple dose ORI regimens are not approved indications.
- **Limitations of Registry.** Data collected during the course of CHROME include the retrospective, noncomparative, unblinded, and nonrandomized nature of the data. Assessment of efficacy was based on a subjective assessment extracted from the medical record by the investigators. Missing data may have been encountered given the 30-day clinical assessment and 60-day safety evaluation windows. Quality checks of data were performed remotely.

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