IDWeek 2018
Poster #1356

Improvement in Quality of Life for Adults with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Following Treatment with Omadacycline or Linezolid

Evan Tzanis, BA[1]; Surya Chitra, PhD[1]; Marla Curran, DrPH[1]; Paul C. McGovern, MD[1]; Jordan Hinahara, BA[2]; Thomas F. Goss, Pharm.D[2]

[1]Paratek Pharmaceuticals, Inc., King of Prussia, PA, USA; [2]Boston Healthcare Associates, Inc., Boston, MA, USA

Contact Information:
Paratek Pharmaceuticals, Inc.
1000 First Avenue, Suite 200
King of Prussia, PA 19406
medinfo@paratekpharma.com

ABSTRACT

Background: The appearance of multi-drug resistant Gram-positive bacteria is a major challenge in clinical care. Omadacycline is the first aminomethylcycline antibiotic (semisynthetic compounds related to tetracyclines) in late-stage clinical development for acute bacterial skin and skin structure infections (ABSSSI), and demonstrates potent *in vitro* activity against many pathogens. However, nausea and vomiting are well-known adverse effects of the tetracycline class

Methods: 735 subjects were enrolled in the OASIS-2 randomized controlled trial comparing oral omadacycline and linezolid for the treatment of adult subjects with ABSSSI known or suspected to be due to a Gram-positive pathogen, with 368 and 367 enrolled in each group, respectively. Subjects completed the 36-Item Short Form Health Survey Version 2 (SF-36v2®), a validated questionnaire on physical and mental health, at both screening and post-treatment evaluation. Results of the SF-36v2 were analyzed in accordance with established norm-based analytic standards for the survey for the intent-to-treat population

Results: Subjects who received omadacycline experienced a 3.25 point mean improvement in overall physical health (p<0.001) and reported significant improvements across all but one component parameter of overall physical and mental health, including physical functioning, bodily pain, role physical, vitality, role emotional, mental health, and social functioning. In contrast, while overall physical health improved for subjects who received linezolid, the improvement in vitality, role emotional, and mental health was not significant. Although omadacycline achieved greater increase from baseline than linezolid across all domains analyzed, the difference in scores was not statistically significant at the p<0.05 level

Conclusions: Omadacycline provides significant improvement in the physical component of quality of life over baseline for adult subjects with ABSSSI known or suspected to be due to a Gram-positive pathogen. Although the OASIS-2 trial was neither designed nor powered to measure differences in quality of life following treatment, trends identified in this analysis merit further investigation

BACKGROUND

- Multi-drug resistant Gram-positive bacteria present a major challenge for clinical care
- Omadacycline is the first aminomethylcycline antibiotic, a semi-synthetic compound related to tetracyclines, in late-stage clinical development for treatment of acute bacterial skin and skin structure infections (ABSSSI)[1,2]
- Omadacycline overcomes the two main mechanisms of tetracycline resistance (efflux pumps and ribosomal protection)[3] and has demonstrated potent *in vitro* activity against Gram-positive aerobes, including methicillin-resistant *Staphylococcus aureus*, many Gram-negative aerobes, anaerobes, and atypical bacterial pathogens[4,5]
- In the previous **O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy (OASIS-1), intravenous followed by oral administration of omadacycline demonstrated non-inferior efficacy to linezolid[6]
- Adverse effects from medications can negatively affect patient health-related quality of life, including impacts on physical health and mental well-being[7]
- Gastrointestinal disorders are frequently reported adverse effects from omadacycline and tetracycline antibiotics[4,8]
- In this analysis, we used the results of the Phase 3 randomized controlled OASIS-2 study to assess impacts of omadacycline versus linezolid treatment for ABSSSI on health-related quality-of-life measures

METHODS

Study Design

- Randomized, double-blind, double-dummy, active comparator controlled, Phase 3 clinical study comparing omadacycline and linezolid for treatment of adult subjects with ABSSSI that is known or suspected to be due to a Gram-positive pathogen
- Subjects were eligible for enrollment in the trial if they were aged ≥18 years, had qualifying ABSSSI with primary lesions ≥75 cm^2, and evidence of systemic inflammatory response within 24 hours prior to randomization
- Eligible subjects were randomized 1:1 to receive either 450 mg omadacycline orally once daily for two doses followed by 300 mg orally once daily, or 600 mg linezolid orally twice daily for a total of 7-14 days
  - Randomization was stratified by type of infection (wound infection, cellulitis/erysipelas, and major abscess [limited to ≤30% of subjects]), and receipt of a single dose of allowed antibiotic therapy within 72 hours prior to dosing (limited to ≤25% of subjects)

Study Measure

- Subjects were asked to complete the 36-item Short Form Health Survey Version 2 (SF-36v2®, Optum Inc., MN, USA) at screening and post-treatment evaluation (PTE; 7-14 days after last dose)
  - The survey was a validated questionnaire assessing overall physical and mental health, including questions on the following sub-topics: physical functioning, bodily pain, role physical, general health, vitality, social functioning, mental health, and role emotional

Data Analyses

- Descriptive analyses of subject demographics were conducted at baseline
- Results of the SF-36v2 survey were analysed in accordance with established norm-based standards for the survey[9]
  - In norm-based scoring, each scale is scored to have the same average (50 points) and the same standard deviation (10 points)
- Analysis was performed on the survey results for the intent-to-treat (ITT) population (all randomized subjects)

RESULTS

- In total, 735 subjects were enrolled: 368 in the omadacycline group and 367 in the linezolid group
- Baseline demographics and characteristics were broadly similar between the two groups (**Table 1**)

Table 1. Subject Demographics and Baseline Characteristics (ITT population)

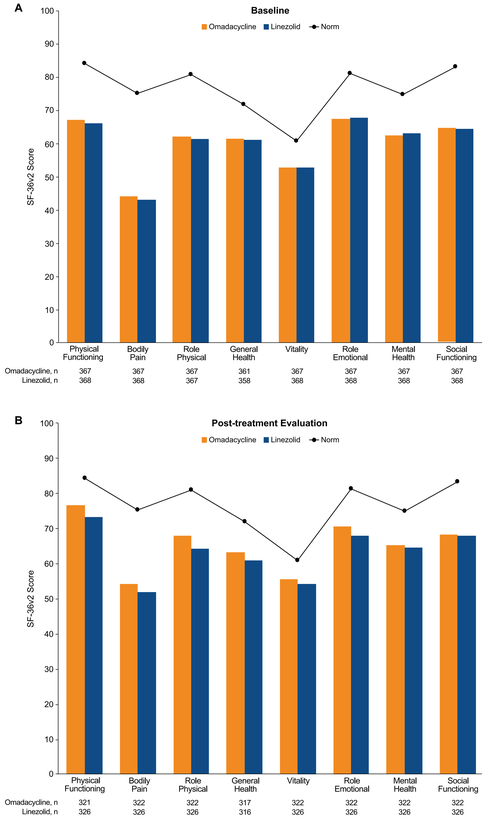
Baseline Characteristic	Omadacycline (N=368)	Linezolid (N=367)
Gender, n (%)		
Male	242 (65.76)	220 (59.95)
Female	126 (34.24)	147 (40.05)
Age, Years		
Mean (95% CI)	42.80 (41.50-44.11)	44.53 (43.19-45.88)
BMI, kg/m²		
Mean (95% CI)	27.91 (27.24-28.57)	27.93 (27.25-28.60)
Infection Type, n (%)		
Cellulitis/erysipelas	86 (23.37)	86 (23.43)
Major abscess	64 (17.39)	64 (17.44)
Wound infection	218 (59.24)	217 (59.13)
Intravenous Drug Use, n (%)		
Yes	256 (69.57)	244 (66.49)
No	112 (30.43)	123 (33.51)
History of Diabetes, n (%)		
Yes	15 (4.08)	32 (8.72)
No	353 (95.92)	335 (91.28)
Total Duration of Exposure on Therapy, Days		
Mean (SD)	8.2 (2.77)	8.0 (2.98)

BMI = body mass index; CI = confidence interval; ITT = intent-to-treat; SD = standard deviation

RESULTS

- At baseline, the highest mean SF-36v2 scores were seen across both treatment groups in physical functioning and role emotional, with lowest scores in vitality and bodily pain (**Fig. 1A**)
- By PTE, scores had improved across all parameters for the omadacycline group, and for physical functioning, bodily pain, role physical, mental health, and social functioning for the linezolid group (**Fig. 1B**)

Figure 1. SF-36v2 Scores at Baseline and PTE (ITT Population)

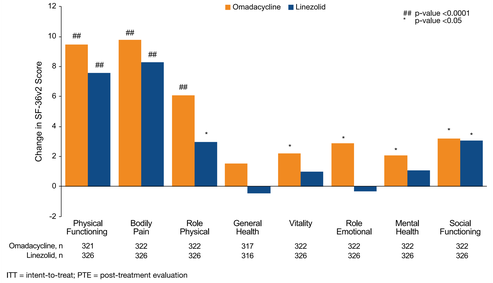


ITT = intent-to-treat; PTE = post-treatment evaluation

RESULTS

- In the omadacycline group, significant increases in SF-36v2 scores from baseline were observed across all but one parameter of physical and mental health (**Fig. 2**)
- In contrast, significant changes from baseline were only observed for the physical functioning, bodily pain, role physical, and social functioning parameters in the linezolid group (**Fig. 2**)

Figure 2. Change in SF-36v2 Scores from Baseline to PTE (ITT Population)

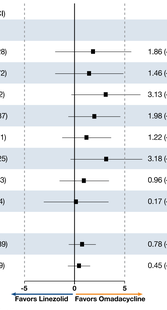


ITT = intent-to-treat; PTE = post-treatment evaluation

- Overall, subjects receiving omadacycline had a mean overall 3.25 point improvement in the physical health SF-36v2 score component, compared with a 2.81 point improvement for the linezolid group (**Fig. 3**)
- For the mental health component, subjects receiving omadacycline had a small 0.20 (95% CI:-0.8 to 1.2) point improvement, compared to a 0.58 (95% CI:-1.5 to 0.4) decrease in score in the linezolid group (**Fig. 3**). The percentage point difference from baseline favored omadacycline by 0.78 points but was not statistically significant (p=0.27)

Figure 3. Comparison of Change in SF-36v2 Parameter Scores from Baseline to PTE for Omadacycline and Linezolid (ITT Population)

Subgroup	Omadacycline Change from baseline (95% CI)	Linezolid Change from baseline (95% CI)	Percentage-point Difference from Baseline (95% CI)	p-value
SF36v2 Scale Parameters:				
Physical Functioning	9.44 (6.76 to 12.13)	7.58 (4.88 to 10.28)	1.86 (-1.95 to 5.67)	0.34
Bodily Pain	9.77 (7.37 to 12.17)	8.31 (5.89 to 10.72)	1.46 (-1.94 to 4.87)	0.40
Role Physical	6.09 (3.64 to 8.53)	2.96 (0.50 to 5.42)	3.13 (-0.34 to 6.60)	0.08
General Health	1.52 (-0.33 to 3.37)	-0.46 (-2.30 to 1.37)	1.98 (-0.63 to 4.59)	0.14
Vitality	2.19 (0.46 to 3.92)	0.97 (-0.77 to 2.71)	1.22 (-1.23 to 3.68)	0.33
Role Emotional	2.88 (0.34 to 5.42)	-0.30 (-2.86 to 2.25)	3.18 (-0.42 to 6.78)	0.08
Mental Health	2.05 (0.32 to 3.78)	1.09 (-0.65 to 2.83)	0.96 (-1.50 to 3.42)	0.44
Social Functioning	3.21 (0.92 to 5.50)	3.04 (0.74 to 5.34)	0.17 (-3.08 to 3.41)	0.92
Norm Based-SF36v2 Summaries:				
Mental Component Summary	0.20 (-0.77 to 1.17)	-0.58 (-1.54 to 0.39)	0.78 (-0.59 to 2.14)	0.27
Physical Component Summary	3.25 (2.46 to 4.05)	2.81 (2.02 to 3.59)	0.45 (-0.67 to 1.57)	0.43



CI = confidence interval; ITT = intent-to-treat; PTE = post-treatment evaluation

RESULTS

- Although omadacycline achieved greater increases from baseline than linezolid across all the parameters analyzed, the difference in scores was not statistically significant at the p<0.05 level (**Fig. 3**)

CONCLUSIONS

- In the OASIS-2 study, omadacycline provided significant improvement in the physical components of quality of life, compared with baseline, for adult subjects with ABSSSI caused by a known or suspected Gram-positive pathogen
- Subjects receiving omadacycline showed greater improvements in all quality-of-life parameters measured, compared to subjects receiving linezolid, although the differences were not statistically significant
- As the OASIS-2 study was not specifically designed or powered to assess quality-of-life outcomes, the trends identified in this analysis warrant further investigation

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FUNDING AND DISCLOSURES

This work was sponsored by Paratek Pharmaceuticals, Inc. Medical editorial assistance, funded by Paratek Pharmaceuticals, Inc., was provided by Innovative Strategic Communications.

ACKNOWLEDGMENTS

The authors wish to thank the subjects and investigators involved in the OASIS-2 study.

Presented at: IDWeek, October 3-7, 2018, San Francisco, CA, USA