Pharmacodynamics of the Long Acting Echinocandin, CD101, in the Neutropenic Invasive Candidiasis Murine Model Using an Extended Interval Dosing Design

Alexander J. Lepak¹, Miao Zhao¹, B. VanScoy², Paul G. Ambrose², and David R. Andes¹,³.

¹Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
²Institute for Clinical Pharmacodynamics, Schenectady, NY, USA
³Department of Medical Microbiology and Immunology, University of Wisconsin, Madison WI, USA

Running Title: CD101 Pharmacodynamics against Candida species

Key Words: Candida, Pharmacodynamics, Antifungal therapy
ABSTRACT

Echinocandins are important in the prevention and treatment of invasive candidiasis but limited by current dosing regimens that include daily intravenous administration. The novel echinocandin CD101 has a prolonged half-life of approximately 130 h in humans making it possible to design once-weekly dosing strategies. The current study examined the pharmacodynamic activity of CD101 using the neutropenic invasive candidiasis mouse model against select C. albicans (n=4), C. glabrata (n=3), and C. parapsilosis (n=3) strains. The CD101 MIC ranged from 0.03 – 1 mg/L. Plasma pharmacokinetic measurements were performed from uninfected mice after intraperitoneal administration of 1, 4, 16, and 64 mg/kg. The elimination half-life was prolonged at 28 – 41 h. Neutropenic mice were infected with each strain by lateral tail vein injection, treated with a single dose of CD101, and monitored for 7 days at which time organism burden was enumerated from the kidneys. Dose-dependent activity was observed for each organism. The PK/PD index AUC/MIC correlated well with efficacy ($R^2$ 0.74 – 0.93). The median stasis 24-h free drug AUC/MIC targets were: C. albicans 2.92, C. glabrata 0.07, and C. parapsilosis 2.61. The PK/PD targets for 1-log$_{10}$ kill endpoint were 2-4-fold higher. Interestingly, the aforementioned PK/PD targets were numerically lower for all three species compared to other echinocandins. In summary, CD101 is a promising, novel echinocandin with advantageous pharmacokinetic properties and potent in vivo pharmacodynamic activity.
INTRODUCTION

Invasive candidiasis is the most common fungal infection in hospitalized patients, the fourth most common cause of nosocomial blood stream infection, and is associated with unacceptably high morbidity and mortality (10, 15-17, 21). Echinocandins, which inhibit cell wall glucan synthesis, were a major development in antifungal therapy. In addition to enhanced spectrum over triazole therapy, studies have demonstrated efficacy for the prevention and treatment of invasive candidiasis (5, 7, 11, 16, 18, 25, 27, 29). They also are associated with very low incidents of adverse effects and have an excellent safety-profile. The combination of spectrum, efficacy and safety is especially important as epidemiological shifts in the causative Candida species has occurred in many parts of the world. Non-albicans species are implicated in more than one-half of all cases of invasive candidiasis and decreased triazole susceptibility to antifungal agents (e.g. C. glabrata) is increasingly recognized (10, 21).

CD101, a novel echinocandin, is a once-weekly intravenous formulation under development for treatment and prevention of systemic fungal infections including invasive candidiasis. It is a chemical analog of anidulafungin, but has toxicological and pharmacokinetic advantages including a terminal half-life of approximately 130 h in humans allowing for extended interval dosing (26). It also demonstrates enhanced in vitro potency compared to other echinocandins against azole- and echinocandin-resistant Candida isolates (24).

The current studies included pharmacokinetic/pharmacodynamic (PK/PD) evaluation of CD101 efficacy in a neutropenic mouse model of disseminated candidiasis to assist with further clinical development of optimal dosing strategies. The studies
were specifically designed to examine the [1] PK of extended interval dosing in the
mouse model; [2] CD101 dose-response relationships against a diverse group of strains
including \( C. \) \textit{albicans}, \( C. \) \textit{glabrata}, and \( C. \) \textit{parapsilosis}; and [3] PK/PD target exposures
associated with efficacy against each species.

\textbf{RESULTS}

\textbf{In vitro susceptibility studies.} The MICs of CD101 for the selected strains are shown
in Table 1. Additionally, given the similarity of CD101 to anidulafungin, the comparative
MICs to anidulafungin are shown. Of note, the strains included those with known
resistance (\( C. \) \textit{glabrata} 10956 is echinocandin-resistant secondary to FKS mutation
\textit{FKS2}_\textit{HS1}_F659V) or reduced susceptibility (\( C. \) \textit{glabrata} 35315) to echinocandins.
Overall, the CD101 MIC varied by 32-fold for all strains.

\textbf{Pharmacokinetics.} The time course of plasma concentrations of CD101 in mice after
IP doses of 1, 4, 16, and 64 mg/kg are shown in Figure 1. Peak (Cmax) levels ranged
from 2.6 – 76.7 mg/L, AUC\(_{0-\infty}\) 93.2 – 40464 mg*h/L, and elimination half-life ranged from
28 – 41 h. The AUC\(_{0-\infty}\) was linear (\( R^2 = 1 \)) over the dose range.

\textbf{Treatment efficacy and pharmacodynamic target determination of CD101.} At the
start of therapy, mice had 4.2 ± 0.2 \( \log_{10} \) CFU/kidney and burden increased in untreated
controls to 7.2 ± 0.6 \( \log_{10} \) CFU/kidney. The \textit{in vivo} dose-response curves for each
group of organisms is shown in Figure 2. Dose-dependent activity was observed with
each group with marked potency at high doses against \( C. \) \textit{albicans} and \( C. \) \textit{glabrata} as a
>2-log_{10} kill was observed against a number of strains. Potency was less pronounced against *C. parapsilosis* although, based on the dose-response curve, we speculate higher doses would have achieved similar activity for this species. The relationship between the PK/PD parameter AUC/MIC over the treatment period (168 h) and treatment effect is shown in **Figure 3**. Both free and total drug concentrations are shown with the best-fit line based on the Hill equation. The coefficients of determination ($R^2$) were strong ranging from 0.74 – 0.93. Finally, shown in **Figure 4** is the average 24-h free drug AUC/MIC in order to augment comparison with previous echinocandin studies which have focused on 24-h PK/PD targets.

The doses necessary to achieve net stasis and 1-log_{10} kill (when endpoint was achieved) are shown in **Table 2**. The corresponding total and free drug AUC/MIC values for the stasis and 1-log_{10} kill endpoints are shown for the total experiment duration of 168 h (7 d). As above, also shown in the table is the average 24-h free drug AUC/MIC targets to allow for comparison to other echinocandin studies in this model. Stasis was achieved against all but a single strain and 1-log_{10} kill was achieved against all *C. albicans* and *C. glabrata* but none of the *C. parapsilosis* strains. The median stasis free drug AUC_{0-168}/MIC targets for each organism group was: *C. albicans* 20.5, *C. glabrata* 0.5, and *C. parapsilosis* 18.2 (only two strains achieved the endpoint). The median stasis 24-h free drug AUC/MIC targets were: *C. albicans* 2.92, *C. glabrata* 0.07, and *C. parapsilosis* 2.61. The PK/PD targets for 1-log_{10} kill endpoint were 2-4-fold higher than stasis targets indicating a relatively steep exposure-response relationship.

**DISCUSSION**
The major limiting factors in echinocandin use are that they have very low oral bioavailability, making their use restricted to IV administration, and need to be administered daily. Therefore, prolonged use for either treatment or prophylaxis comes with risk of IV complication such as thrombosis or line-related sepsis, as well as the need for patients to access the health care setting on a frequent basis adding risk of health care associated infection and increased health system costs. CD101 is a novel echinocandin with distinctive PK advantages that include a prolonged elimination half-life of 125-146 h in humans (26). This allows for once-weekly, or possibly even more infrequent, dosing regimens. The potential advantages are numerous. First, extended-dosing regimens could mitigate ongoing risks of chronic, indwelling IV access devices. Secondly, it would decrease health care access, which would decrease risk of health care associated complications and likely increase patient satisfaction. Third, it has the potential to decrease health care costs given the decreased number of infusions that would be necessary. In sum, successful development of CD101 would permit weekly outpatient echinocandin dosing in the treatment setting, similar to the many advantages that have been noted with development of the long-acting antibacterials oritavancin and dalbavancin, while also allowing for once-weekly outpatient prophylaxis with an echinocandin, particularly in vulnerable transplant patients.

In the current mouse model pharmacodynamic study, we aimed to integrate the PK properties and in vitro potency to provide guidance on pharmacodynamic targets associated with efficacy against a clinically relevant and diverse group of Candida spp. Indeed, the PK of CD101 were unique in that the elimination half-life in mice was prolonged (range 29-41 h). For comparison purposes, the half-lives of other
137 echinocandins in the same mouse model are on average approximately 14 h (2, 4). We
138 also demonstrated promising in vitro potency against Candida spp. similar to previous
139 larger surveillance antimicrobial susceptibility studies (9, 22-24). Finally, we
140 demonstrated CD101 has favorable in vivo efficacy using the murine disseminated
141 candidiasis model with numerically lower PK/PD target exposures for most organisms
142 compared to other echinocandins. For example, the median stasis 24-h free drug
143 AUC/MIC against C. albicans was 2.92. This is 5- to 10-fold lower than caspofungin,
144 micafungin, and anidulafungin targets against this species (1). An even larger
145 difference was demonstrated for C. glabrata where CD101 free AUC/MIC targets were
146 >10-fold lower than the three comparator echinocandins (1). Candida parapsilosis
147 PK/PD target analysis was limited in the current study as only two strains were
148 evaluable for the stasis target endpoint, but here too CD101 free AUC/MIC targets were
149 numerically lower than comparator echinocandins (1). Additionally, due to the
150 prolonged half-life, mice were protected from organism growth and disease for a
151 neutropenic duration of 7 days. It is important to note the current studies differed from
152 previous echinocandin studies in this model in experimental duration (7-day
153 experiments vs. 24-hour experiments). Therefore, PK/PD target differences noted in
154 this study could be due to study design, especially in light of a recently published study
155 that demonstrated the shape of the CD101 drug exposure influences efficacy (12).
156 Taken together, the study demonstrates that CD101 is a potential valuable addition to
157 the antifungal armamentarium given its unique PK properties and in vivo efficacy.
158 An important consideration in translating preclinical PK/PD target models to
159 clinical medicine is to examine the targets identified in the context of human PK and
surveillance susceptibility ranges. Pharmacokinetic study of CD101 in humans demonstrated a steady state free drug AUC\textsubscript{0-16h} of 1840 mg*h/L for a 400 mg dose and 813 mg*h/L for a 200 mg dose. This would translate into an average 24-h AUC of approximately 47.8 and 6.8 mg*h/L, respectively, over a 7-day period\textsuperscript{(26)}. Thus, if a patient were to receive 400 mg of CD101 on day 1 followed by 200 mg on day 8 to complete two weeks of therapy, the stasis target would be expected to be achieved against all \textit{C. albicans} and \textit{C. parapsilosis} isolates with MIC ≤ 1 mg/L and against all \textit{C. glabrata} with MIC ≤ 16 mg/L. The potency against \textit{C. glabrata}, including an \textit{FKS} mutant strain included in this study, deserves particular attention to further study given the rise of echinocandin resistance within this species. Overall, the data suggest CD101 exposures in humans would be expected to meet or exceed the stasis targets identified in this study for nearly all wild-type isolates of the examined species\textsuperscript{(9, 22-24)}. While this helps to define potential MIC breakpoints, further clinical PK study of CD101 in patients combined with Monte-Carlo analysis will be important to substantiate target achievement and MIC breakpoints for CD101.

In summary, CD101 is a promising, novel echinocandin in development with advantageous PK properties allowing for once-weekly dosing strategies, which would mitigate risks to patients, conserve health care resources and potentially lower expenditures, and allow for extended outpatient access to echinocandin treatment and prophylaxis. CD101 has demonstrable \textit{in vitro} and \textit{in vivo} potency that is either equivalent to or an improvement upon comparator echinocandins, especially in regards to \textit{C. glabrata}. Single doses of CD101 provided 7 days of potent antifungal activity in a well-established immunocompromised disseminated candidiasis model. Importantly,
the PK/PD targets identified suggest that current studies of intermittent dosing strategies (i.e. once-weekly infusions) of CD101 are likely to be efficacious in humans against the majority of *C. albicans*, *C. glabrata*, and *C. parapsilosis* strains. The studies indicate that continued clinical evaluation and development for the treatment and prevention of invasive candidiasis, as well as other potential fungal infections, should be pursued.

**MATERIALS AND METHODS**

**Antifungal agent.** CD101 was supplied by Cidara Therapeutics, Inc (San Diego, CA).

Drug dose solutions were prepared on the day of experimentation according to manufacturer instructions with 0.9% NaCl, 10% DMSO and 1% Tween-20.

**Strains.** Ten clinical *Candida* strains were used for the *in vivo* treatment studies, including four *C. albicans*, three *C. glabrata*, and three *C. parapsilosis* strains (Table 1). This group was selected to encompass phenotypic variability in susceptibility to triazoles and echinocandins and was based on similar fitness in the animal model as defined by the amount of growth in control animals over 24 h. The organisms were maintained, grown, and quantified on Sabouraud's dextrose agar (SDA) plates.

**In vitro susceptibility testing.** All isolates were tested in accordance with the standards in CLSI document M27-A3 (6). The MICs were determined visually after 24 h of incubation as the lowest concentration of drug that causes a significant diminution
(≥50%) of growth compared to controls. MICs were determined on three separate occasions in duplicate. Results are expressed as the median of these results.

**Animals.** Six-week-old ICR Swiss/CD1 specific-pathogen-free female mice (Harlan Sprague-Dawley, Indianapolis, IN) weighing 23 to 27 g were used for all the studies. The animals were maintained in accordance with American Association for Accreditation of Laboratory Care criteria (14). The animal studies were approved by the Animal Research Committee of the William S. Middleton Memorial Veterans Affairs Hospital and the University of Wisconsin.

**Infection model.** A neutropenic, mouse, disseminated candidiasis model was used for the treatment studies. The mice were rendered neutropenic (polymorphonuclear cell count, <100/mm³) by injecting 150 mg/kg of cyclophosphamide (Mead Johnson Pharmaceuticals, Evansville, IN) subcutaneously 4 days before infection, 100 mg/kg of cyclophosphamide 1 day before infection, and additional cyclophosphamide doses (100 mg/kg) on day 2 and day 4 after infection to ensure neutropenia throughout the 168-h (7-d) study period. Three mice were included in each treatment and control group.

The organisms were subcultured on SDA plates 24 h prior to infection. The inoculum was prepared by placing 3 to 5 colonies into 5 ml of sterile pyrogen-free 0.15 M NaCl warmed to 35°C. The final inoculum was adjusted to a 0.6 transmittance at 530 nm. The fungal count of the inoculum determined by viable counts on SDA was 6.1 ± 0.2 log₁₀ CFU/ml.
Disseminated infection with the *Candida* strains was achieved by injection of 0.1 ml of the inoculum via the lateral tail vein 2 h prior to the start of antifungal therapy. At the end of the study period, the animals were sacrificed by CO₂ asphyxiation. The kidneys of each mouse were aseptically removed and placed in 0.15 M NaCl at 4°C. The kidneys were homogenized and serially diluted 1:10, and the aliquots were plated onto SDA for viable fungal colony counts after incubation for 24 h at 35°C. The lower limit of detection was 100 CFU/ml. The results are expressed as the mean CFU/kidney for three mice.

**Pharmacokinetics.** Single-dose PK evaluation was undertaken following intraperitoneal (IP) doses of 1, 4, 16, and 64 mg/kg of CD101. Plasma from groups of three mice per time point (1, 3, 6, 12, 24, 48 and 72-h) was collected. The plasma drug concentrations were determined by liquid chromatography-tandem mass spectrometry. A noncompartmental model was used in the PK analysis. Elimination half-life was calculated by nonlinear least-squares technique. The area under the concentration-time curve (AUC) was calculated by the trapezoidal rule. Pharmacokinetic exposures for doses not directly measured in the PK study were estimated by linear extrapolation for higher and lower dose levels and by interpolation for dose levels within the dose range studied given the linear PK results. Protein binding (99.2%) was based on a report of binding in mice from the sponsor (12).

**Treatment efficacy and pharmacodynamic target determination of CD101.** Neutropenic mice were infected with one of 10 *Candida* strains as described above. The
dosing regimens were chosen to vary the magnitude of the 24-h AUC/MIC index and to attempt to produce treatment effects that ranged from no effect to a maximal effect. Five dose levels that varied from 0.25 to 64 mg/kg were administered once in a 0.2-ml volume by IP route for the 168-h study period. Due to enhanced effect against a single isolate, additional studies at 0.0156 and 0.0625 mg/kg were performed for C. glabrata 5592. Groups of three mice were used for each dosing regimen and control group. At the end of the treatment period (168 h), the mice were euthanized, and their kidneys were immediately processed for CFU determination as described above.

Data analysis. A sigmoid dose-effect (Hill) model was used to measure the in vivo potency of CD101. The efficacy endpoints included the dose level required to produce a 24-h net static effect (no change in organism burden compared to that at the start of therapy) and the dose required to achieve a 1-log$_{10}$ reduction in colony counts (relative to the burden at the start of therapy), when achieved. The maximum response ($E_{\text{max}}$) was measured as the difference in the number of CFU/kidney relative to that of the untreated control animals. The doses associated with the stasis and 1-log$_{10}$ endpoint for each strain was calculated using the equation: $\log_{10} D = [\log_{10} (E/(E_{\text{max}} - E))/N] + \log_{10} ED_{50}$, where $D$ is the drug dose, $E$ is the control growth in untreated animals, $E_{\text{max}}$ is the maximal effect, $N$ is the slope of the dose-response relationship, and $ED_{50}$ is the dose needed to achieve 50% of the maximal effect. The associated AUC/MIC targets were then calculated for each strain. We used the PK/PD index AUC/MIC in this study as it has been shown to be associated with treatment efficacy in previous in vivo studies of echinocandins (1-4, 8, 13, 19, 20, 28). The calculations were performed using both total
and free drug concentrations. The coefficient of determination ($R^2$) was used to estimate the variance that might be due to regression with the PK/PD index. Kruskal-Wallis one-way analysis of variance (ANOVA) was used to determine if the differences in PK/PD targets were significant between the species.

ACKNOWLEDGEMENTS

This study was supported by funding from Cidara Therapeutics, Inc.

REFERENCES


Figure Legends:

**Figure 1.** Plasma concentrations of CD101 in mice following single IP doses. Samples were obtained at seven time points over 72 hours. Each symbol represents the mean and standard deviation from three mice. Cmax represents the peak concentration, AUC is from 0 to infinity, and T1/2 the beta elimination half life.

**Figure 2.** CD101 dose-response curves against C. albicans (A), C. glabrata (B), and C. parapsilosis (C). Groups of three mice were administered single IP doses ranging from 0.0156 – 64 mg/kg. Experiment duration was 7 days after which time mice were sacrificed and infectious burden in the kidneys enumerated. Each symbol represents the mean and standard deviation from three mice. The horizontal dashed-line at 0 represents the burden of organisms in the kidneys of mice at the start of therapy. Data points below the line represent cidal activity and points above the line represent net growth.

**Figure 3.** Relationship between total and free drug AUC/MIC and treatment effect for C. albicans (A), C. glabrata (B), and C. parapsilosis (C). AUC is measured as the total (red symbols) or free (blue symbols) AUC over the full treatment course (168 h). Each symbol represents the mean fungal burden from three mice. The horizontal dashed-line at 0 represents the burden of organisms in the kidneys of mice at the start of therapy. Data points below the line represent cidal activity and points above the line represent net growth. The curved line through the data is the best fit line based on the hill equation and the co-efficient of determination ($R^2$) is shown for each organism group.

**Figure 4.** Relationship between average 24-h free drug AUC/MIC (fAUC/MIC) over the treatment duration and treatment effect for C. albicans (A), C. glabrata (B), and C. parapsilosis (C). Each symbol represents the mean fungal burden from three mice. The horizontal dashed-line at 0 represents the burden of organisms in the kidneys of mice at the start of therapy. Data points below the line represent cidal activity and points above the line represent net growth. The curved line through the data is the best fit line based on the hill equation and co-efficient of determination ($R^2$) is shown for each organism group. Also shown is the maximum effect (Emax), 50% maximum effect (ED50), and slope of the line (N).
Table 1. Study organisms, CD101 susceptibility results, and comparative susceptibility results to anidulafungin.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Strain</th>
<th>CD101 MIC (mg/L)</th>
<th>Anidulafungin MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>K-1</td>
<td>0.06</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>580</td>
<td>0.06</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>98-17</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>98-210</td>
<td>0.03</td>
<td>0.015</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>10956</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5592</td>
<td>0.125</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>35315</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>20519.069</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>20477.048</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>20423.072</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>
| Organism     | Strain | M/C (mg/L) | Static dose (mg/kg) | Stasis total drug AUC<sub>50</sub>/MIC | Stasis free drug AUC<sub>50</sub>/MIC | Stasis 24 h log kill dose (mg/kg) | 1 log kill AUC<sub>50</sub>/MIC | Median | Mean | St Dev
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>K-1</td>
<td>0.06</td>
<td>2.52</td>
<td>3197.16</td>
<td>25.58</td>
<td>3.65</td>
<td>5.26</td>
<td>5005.95</td>
<td>18.05</td>
<td>8.86</td>
</tr>
<tr>
<td></td>
<td>580</td>
<td>0.06</td>
<td>3.20</td>
<td>1769.30</td>
<td>14.15</td>
<td>2.02</td>
<td>2.03</td>
<td>2067.21</td>
<td>21.34</td>
<td>3.05</td>
</tr>
<tr>
<td></td>
<td>96-17</td>
<td>0.06</td>
<td>1.34</td>
<td>1918.43</td>
<td>15.35</td>
<td>2.19</td>
<td>2.73</td>
<td>3433.40</td>
<td>27.47</td>
<td>3.92</td>
</tr>
<tr>
<td></td>
<td>99-210</td>
<td>0.03</td>
<td>1.06</td>
<td>3241.65</td>
<td>25.93</td>
<td>3.70</td>
<td>2.28</td>
<td>3475.95</td>
<td>17.01</td>
<td>7.72</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>1.53</td>
<td>2531.64</td>
<td>20.25</td>
<td>2.89</td>
<td>3.08</td>
<td>4495.63</td>
<td>35.97</td>
<td>5.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.27</td>
<td>2557.79</td>
<td>20.46</td>
<td>2.92</td>
<td>2.51</td>
<td>4654.68</td>
<td>37.24</td>
<td>5.32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>St Dev</td>
<td>0.67</td>
<td>796.71</td>
<td>6.37</td>
<td>0.91</td>
<td>1.49</td>
<td>1698.80</td>
<td>13.59</td>
<td>1.94</td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>10956</td>
<td>1</td>
<td>6.29</td>
<td>418.68</td>
<td>3.35</td>
<td>0.48</td>
<td>17.25</td>
<td>1052.22</td>
<td>3.42</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>5592</td>
<td>0.125</td>
<td>0.06</td>
<td>43.16</td>
<td>0.35</td>
<td>0.05</td>
<td>0.43</td>
<td>317.50</td>
<td>2.54</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>35315</td>
<td>0.5</td>
<td>0.34</td>
<td>62.50</td>
<td>0.50</td>
<td>0.07</td>
<td>2.39</td>
<td>367.06</td>
<td>2.94</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>2.23</td>
<td>174.78</td>
<td>1.40</td>
<td>0.20</td>
<td>0.69</td>
<td>578.53</td>
<td>4.63</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.34</td>
<td>62.50</td>
<td>0.50</td>
<td>0.07</td>
<td>2.39</td>
<td>367.06</td>
<td>2.94</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>St Dev</td>
<td>3.52</td>
<td>211.44</td>
<td>1.69</td>
<td>0.24</td>
<td>9.20</td>
<td>416.63</td>
<td>3.29</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>20519.069</td>
<td>1</td>
<td>NA*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20477.048</td>
<td>1</td>
<td>52.96</td>
<td>3339.42</td>
<td>26.72</td>
<td>3.82</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20423.072</td>
<td>0.5</td>
<td>9.62</td>
<td>1217.49</td>
<td>8.74</td>
<td>1.39</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*NA, not achieved