Review Article

Comparison between liposomal formulations of amphotericin B

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Abstract

Given the clinical success of commercial amphotericin B lipid products, investigators have begun making generic formulations of liposomal amphotericin B. Generic medicines are an attractive approach to help decrease the cost and accessibility to healthcare, provided that appropriate studies are performed to ensure bioequivalence with the parent product. This is of particular concern for liposomal drugs such as amphotericin B where liposomes are used as a carrier system to reduce the toxicity of the active agent. A favorable therapeutic profile for this form of the drug has to include the proper chemical composition along with strictly controlled manufacturing processes. Studies have shown that a comparison of liposomal amphotericin B products with different or the same chemical compositions, using different methods of production, will vary in size, and have significantly dissimilar in vitro and in vivo toxicities along with reduced efficacy. These results underscore the importance of establishing appropriate bioequivalence testing for liposome products to ensure uniformity of their therapeutic index.

Key words: amphotericin B, liposomes, bioequivalence, invasive fungal infections, leishmaniasis.

Introduction

Generic medicines are an attractive approach to help decrease the cost and accessibility to healthcare. However, there is concern that generic products may not be bioequivalent to the parent product resulting in different levels of efficacy and tolerability.1–8 This is of particular clinical relevance for liposomal amphotericin B products given the toxicity of the active agent and the availability of generic forms of the drug in countries outside Europe and the United States. To further address this issue, the present review will focus on a comparison of the physicochemical and biological properties of the various amphotericin B liposomal formulations.

Amphotericin B

Mechanisms of therapeutic efficacy

AMB deoxycholate (AMBd) is a broad-spectrum antifungal agent, active against most clinically relevant fungal species, as well as protozoan Leishmania species.9,10 AMB forms complexes with ergosterol in fungal cell membranes and
Table 1. Constituents of liposomal amphotericin B formulations (mg/vial).

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Phosome(\text{a}), AmBi(\text{L}) and Lambin(\text{a})</th>
<th>Ambihep(\text{c}) and Lipholyn(\text{c})</th>
<th>Ampholip(\text{f})</th>
<th>Fungisome(\text{g})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>50</td>
<td>50</td>
<td>5–100</td>
<td>1</td>
</tr>
<tr>
<td>Sucrose</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td></td>
</tr>
<tr>
<td>Hydrogenated soy phosphatidylcholine (HSPC)</td>
<td>213</td>
<td>213</td>
<td>494.8</td>
<td>31.5</td>
</tr>
<tr>
<td>Distearyl phosphatidylglycerol (DSPG)</td>
<td>84</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>52</td>
<td>52</td>
<td>62.8</td>
<td>13.5</td>
</tr>
<tr>
<td>Alpha-tocopherol</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Disodium succinate hexahydrate</td>
<td>27</td>
<td>27</td>
<td></td>
<td>3.4</td>
</tr>
<tr>
<td>Dimyristoryl phosphatidylcholine (DMPC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimyristoryl phosphatidylglycerol (DMPG)</td>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
</tr>
</tbody>
</table>


\(\text{b}\)Product insert for Phosome (Cipla Ltd., 2012).

\(\text{c}\)www.TLCbio.com.

\(\text{d}\)Olson et al., Med Mycol 2015 (reference 2).

\(\text{e}\)Product inserts for Ambihep (Abbott India Ltd., 2013) and Lipholyn (Lyka Labs, 2013).


\(\text{g}\)Romero and Morilla, Expert Opin Drug Deliv 2008.

Lanosterol in cell membranes of some Leishmania spp., creating transmembrane channels, which allow cell components to leak out.11–14 AMB also stimulates the fungus to produce oxygen radicals,13,15 and to modulate macrophage activity by stimulating production of pro-inflammatory cytokines, reactive oxygen intermediates and nitric oxide.16–20

Host toxicities

In clinical use, acute infusion-related reactions and nephrotoxicity often prevent administration of a complete course of AMBd and/or sufficient doses. Infusion-related reactions, including nausea, vomiting, rigors, fever, hypertension or hypotension, and hypoxia, are thought to be caused by the effects of AMB on pro-inflammatory cytokine production.13–19,21 Dose-limiting nephrotoxicity, the principle chronic adverse effect of AMBd, is caused by vasoconstriction and direct interaction with the distal tubule cell membranes.13,22,23 AMB binding to cholesterol in the cell membranes of the distal tubules results in loss of electrolytes, impaired urinary acidification and concentration, and renal tubular acidosis. Continued tubular damage eventually causes a decrease in glomerular filtration rate (GFR) that further constricts the afferent arterioles.13,23

Liposomal amphotericin B products

AmBisome

Mechanisms for reduced host toxicities

The efficacy and safety (i.e., therapeutic index) of any liposomal AMB product is primarily determined by the rate and extent of AMB release from the liposomes upon administration. For AmBisome there are several key physicochemical attributes that have contributed to its favorable therapeutic index. First, the small size of these liposomes (<100 nm) results in prolonged circulation allowing distribution into many different organs.24 Second, its composition (Table 1) ensures that AMB remains associated with the liposome bilayer until it comes into contact with a fungus, minimising the adverse effects of AMB on host tissues. To achieve this, these liposomes are composed of cholesterol that binds with AMB, as well as hydrogenated soy phosphatidylcholine (HSPC) and distearyl phosphatidylglycerol (DSPG) which are stable in the body at 37\(\text{°}C\).24 In addition, the negative charge on the DSPG interacts with the positive amine group of AMB, forming an AMB and DSPG complex in the liposome bilayer. Finally, these liposomes bind to fungal cell walls, followed by their transit through the fungal cell wall to allow the AMB to target to the ergosterol in the fungal cell membrane.25,26

Manufacturing process

The reduced toxicity of AmBisome is dependent on a complex, carefully controlled and precise, multistep, manufacturing process, which is needed to ensure uniformity of the product from batch to batch.1 The quality control assays for AmBisome at each manufacturing step include chemical (HPLC analysis), physical (particle sizing, absence of flocculation and aggregation over time, stability at different temperatures), and biological testing (in vitro activity against different fungi, in vivo toxicity at increasing doses). Studies have demonstrated that even minor alterations in the molar ratio of AMB to phospholipids, changes in the phospholipid fatty acid chain length, or the size and charge...
of the liposomes can affect the association between AMB and the liposome bilayer, altering the product’s toxicity.1,27

Besides the actual liposome components, the method used to make the liposomes will also affect its toxicity. For example, liposomes formed by sonication were found to be more toxic to mice than those produced by homogenisation, even though the liposomes had the same AMB:lipid molar ratios.27 Other studies have shown that various stresses on liposomes, such as sterile filtration during production, filtration prior to use, requirements for refrigeration, lyophilisation conditions, and dilution in infusion diluents, can lead to flocculation, aggregation, leakage of the drug, phase separation, and disintegration of the liposomes.28 Consequently, monitoring of any such changes is required at every manufacturing step to ensure batch reproducibility.

Other liposomal AMB products

There are several other liposomal AMB products currently available outside of Europe and North America, although detailed information for these products in the public domain is limited. They include “Ambisome” (AHPL), Ambihope (Abbott Healthcare Pvt. Ltd.), Ambilip, Amphotin, and Amphotin-LIP (United Biotech), Amif and Ambitas (Intas), Amfocan (Dabur), Ampholip and Amphotret (Bharat Serum), Amphotin-LIP (United Biotech), Amfotex (Alkem/Cytomed), Amfocare (Criticare), Lambin (Sun Pharmaceutical Industries Ltd.), Lypholyn (Lyka Labs Ltd.), Mycol (VHB/ Cytocare), Phoricin (Chandra Bhagat Pharma), Phosome (Cipla), and AmBiL (Taiwan Liposome Co.). Some of these products have the same chemical composition (e.g., AmBisome, Phosome, AmBiL and Lambin) (Table 1), but studies have shown that this does not necessarily translate into equal efficacy and safety1,2 suggesting that different manufacturing processes can alter the properties of the final liposome product. Other formulations including Ambihope, Lipholyn, Ampholip and Fungisome vary in their components (Table 1) and methods of production. For example, with Fungisome, the product is made as multilamellar vesicles (MLVs) which require ultrasonication for 45 minutes prior to infusion to produce the small unilamellar vesicles (SUVs) suitable for therapy.29,30 This approach for Fungisome was based on preliminary studies that compared MLVs with SUVs. The results indicated that compared to the MLV form, the SUVs were less toxic although the efficacy of stored SUVs decreased over time.29 In comparison, Ampholip is a ribbon-like structure which settles out of solution and gets dispersed uniformly on mild shaking (bharatserums.com: package insert).

Pre-clinical studies comparing different liposomal amphotericin B products

In vitro MIC assays of these products have shown that they can have similar or different activity against yeast, filamentous fungi, and dimorphic fungi since the mean and range of MICs varies depending upon the strain being tested and the type of in vitro assay used.31–35 In contrast, in vivo evaluation of efficacy and toxicity in animal models has indicated some definite essential differences between the products.

The critical importance of controlling the way the product is manufactured can be seen in pre-clinical studies comparing AmBisome with two other liposomal AMB products, Anfogen® (Genpharma, S.A., Argentina) and Lambin® (Sun Pharmaceutical Industries Ltd.)1,2 that have the same chemical composition as AmBisome. Anfogen was originally marketed in Argentina but withdrawn due to toxicity concerns and Lambin is currently marketed in India. As seen in Table 2, AmBisome was markedly smaller (30–36%) than the other two agents. A much higher dose of AmBisome was needed to damage RBC as indicated by K+ leakage from the RBC. The K+ leakage test is used as a
sensitive in vitro assay for evaluating amphotericin B toxicity. With in vivo testing, AmBisome was also significantly less toxic based on single intravenous LD50 dosing studies and with daily dosing, there was significantly less renal tubular necrosis. Mice with pulmonary aspergillosis survived longer with AmBisome treatment and based on histopathology, there was less infection in the lungs. These results show that differences in the processing conditions with products that have the same chemical composition can have a pronounced effect on the functional characteristics of the drug.

In another preclinical study, radiolabeled (99m Tc) Fungisome and radiolabeled pegylated liposomal amphotericin B were compared in a drug biodistribution study in Balb/c mice. Liver uptake of the pegylated liposomal amphotericin B formulation was 67% at 0.5 hour post-injection and 73% at 24 hour post-injection. In comparison, radiolabeled Fungisome liver uptake was 81% and 11% at 0.5 and 24 hours post-injection, respectively. Uptake of both drugs in the kidneys was similar with 8.2% (0.5 hour post-injection) and 0.4% (24 hours post-injection) for the pegylated liposomal amphotericin B and 5.7% (0.5 hour post-injection) and 0.9% (24 hours post-injection) for the radiolabeled Fungisome.

### Table 3. Comparative AmBisome clinical studies for the treatment of IFIs.

<table>
<thead>
<tr>
<th>Category</th>
<th>Study design</th>
<th>Patients</th>
<th>Treatment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive candidiasis</td>
<td>Prospective, double-blind, RCT</td>
<td>531 adults (≥ 16 years) with confirmed IC or candidaemia</td>
<td>AmBisome 3 mg/kg/day vs micafungin 100 mg/day</td>
<td>39</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>Prospective, double-blind, RCT</td>
<td>339 immunocompromised adults and children (≥30 days old) with proven or probable IFIs (EORTC/MSG criteria)</td>
<td>AmBisome 3 mg/kg/day vs AmBisome 10 mg/kg/day</td>
<td>40</td>
</tr>
<tr>
<td>CNS cryptococcosis</td>
<td>Prospective, double-blind, RCT</td>
<td>267 adults and children (≥1 month) with AIDS-associated acute cryptococcal meningitis</td>
<td>AmBisome 3 or 6 mg/kg/day vs AMBd 0.7 mg/kg/day</td>
<td>41</td>
</tr>
<tr>
<td>Disseminated histoplasmosis</td>
<td>Prospective, double-blind, RCT</td>
<td>28 HIV-infected adults (≥18 years) with a primary episode of cryptococcal meningitis</td>
<td>AmBisome 4 mg/kg/day vs AMBd 0.7 mg/kg/day</td>
<td>42</td>
</tr>
<tr>
<td>Empiric antifungal therapy</td>
<td>Prospective, double-blind, RCT</td>
<td>687 neutropaenic (&lt;500/mm³) patients (2–80 years) with persistent FUO despite broad-spectrum antibiotics</td>
<td>AmBisome 3 mg/kg/day vs AMBd 0.6 mg/kg/day</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Prospective, double-blind, RCT</td>
<td>244 neutropaenic (&lt;500/mm³) patients (&gt;2 years) with persistent FUO despite broad-spectrum antibiotics</td>
<td>AmBisome 3 mg/kg/day vs AMBd 0.7 mg/kg/day</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Prospective, double-blind, RCT</td>
<td>81 HIV-infected adults (≥16 years) with moderate to severe disseminated histoplasmosis</td>
<td>AmBisome 3 mg/kg/day vs AMBd 0.7 mg/kg/day</td>
<td>43</td>
</tr>
</tbody>
</table>

Abbreviations: IFI: invasive fungal infection; RCT: randomized clinical trial; HIV: human immunodeficiency virus; IC: invasive candidiasis; FUO: fever of unknown origin.

#### Clinical studies with liposomal amphotericin B products

**AmBisome**

**Fungal infections**

A brief review of key AmBisome randomized controlled clinical studies is summarised below and in Table 3.

**Invasive candidiasis (IC).** AmBisome was compared with micafungin in a RCT among 392 patients for treatment of IC and candidaemia, with 90% success in each arm. However, micafungin was better tolerated with respect to renal and electrolyte abnormalities and infusion-related adverse events.

**Invasive aspergillosis (IA).** A randomized clinical trial (RCT) was performed to compare a standard dose of AmBisome (3 mg/kg/day) with a high-loading dose (10 mg/kg/day) in highly immunocompromised patients, most of whom had hematologic malignancies and were neutropenic at baseline. Among the 201 patients with confirmed infection, a favorable response was observed in 50% and 46% of patients for the 3 and 10 mg/kg doses, respectively. As the 10 mg/kg/day regimen demonstrated no additional efficacy benefit with higher rates of...
nephrotoxicity, the study confirmed the efficacy of the 3 mg/kg/day dose as initial therapy for invasive aspergillosis (IA).

**CNS cryptococcosis.** In a RCT for cryptococcosis with 267 eligible patients, AmBisome (3 or 6 mg/kg/day) was compared with AMBd (0.7 mg/kg).41 Efficacy was similar for all three treatment groups, but both dosages of AmBisome produced a significantly lower incidence of infusion-related reactions than AMBd (P < .001), and significantly fewer patients given 3 mg/kg AmBisome developed nephrotoxicity versus AMBd (P = .004). Similar findings have been reported in other studies, such as that conducted by Leenders and coworkers.42

**Disseminated histoplasmosis.** In a RCT comparing AmBisome with AMBd for induction therapy of disseminated histoplasmosis in AIDS patients.43 AmBisome was better tolerated (9% vs 37% nephrotoxicity) and achieved a higher clinical success rate (88% vs 64%) than AMBd. Based on these data, most experts prefer a lipid formulation of AMB due to safety and efficacy concerns with AMBd.44

**Empiric antifungal therapy.** Two large RCTs have evaluated AmBisome versus AMBd or ABLC for empiric treatment in the persistently febrile neutropenic patient.45,46 Although the majority of patients did not have a documented fungal infection, the studies did provide substantive toxicity data. AmBisome at 3 mg/kg and 5 mg/kg daily was associated with significantly lower rates of nephrotoxicity (P < .001) and infusion-related reactions (P < .01) than AMBd (0.6–0.8 mg/kg)45 or ABLC (5 mg/kg).46

**Fungisome**

**Fungal infections**

**Systemic infections (phase II).** In a phase II clinical study to determine Fungisome safety and efficacy, there were 55 evaluable patients with systemic fungal infections.29 Of these patients, those individuals treated with 1 mg/kg/day Fungisome showed complete responses in 32/33 for candidiasis, 6/7 for cryptococcal meningitis, 4/7 for aspergillosis, and 1/1 for cladosporiosis. There were partial responses in four patients; and three patients failed to respond. There was also a significant difference in survival favoring Fungisome since 3 patients treated with amphotericin B and 1 treated with Fungisome died during induction (P = .04). Fungisome was found to be safe at 1 mg/kg/day.

**Systemic infections (phase III).** A clinical comparison of AMBd versus Fungisome was investigated in a phase III clinical study of 34 patients (17 patients/group) with proven systemic fungal infections.29 Fungisome was better tolerated than AMBd at doses of 0.5–2.0 mg/kg with complete responses in 17/17 patients. Those patients treated with AMBd had 14/17 complete responses.

**Systemic infections (Post-marketing clinical study).** A post-marketing retrospective clinical study was performed to evaluate the safety, tolerability and effectiveness of Fungisome in fungal infections.47 The doses used were 1, 2, or 3 mg/kg/day given over a 6 month period with 91/109 assessable patients (86, 9, and 14 patients/dose, respectively). Mild infusion-related adverse events were reported in 40 (36%) of the patients, 11 (10%) of patients had moderate adverse events and 2 (1.8%) had severe adverse events. Complete responses were observed in 67 (73.6%) of the patients with partial responses in 16 (17.5%) and no response in 8 (8.7%) of the patients.

**Empiric treatment.** A multicenter, randomized, controlled clinical trial was performed to demonstrate superiority of Fungisome (1 and 3 mg/kg/day) in comparison to AMBd (1 mg/kg/day) in the empirical treatment of febrile neutropenia.48 The study was performed at two centers in males and females (50 patients per treatment group) between the ages of 2 and 60 years who had febrile (≥38°C) neutropenia (ANC ≤ 500). Assessable patients included 19/22 at 1 mg/kg Fungisome, 20/23 at 3 mg/kg Fungisome, and 18/20 for 1 mg/kg AMBd. There was no statistical difference in efficacy between the groups, but there were less adverse events with Fungisome compared to AMBd. This study was underpowered to detect a significant difference amongst the groups and a larger sample size is warranted. Notably, the low and high doses of Fungisome were equally efficacious and well tolerated, with treatment cost likely limiting the use of the higher dose.

**AmBiL**

**Bioequivalence study (phase I)**

A Bioequivalence phase I study was performed to compare AmBiL versus AmBisome following two IV infusions of 2 mg/ml of the drug in healthy subjects. The study was completed in 2013, but no study results have been posted (NCT01652859, ClinicalTrials.gov). There is also a phase II cryptococcal meningitis clinical trial being performed which was initiated in 2011, with an estimated completion date of 2016. Eligible subjects are randomized into two groups: AmBiL (4 mg/kg/day) or AMBd (1 mg/kg/day) in a 2:1 ratio. The study is being conducted to evaluate the safety and efficacy of these two drugs with or without flucytosine followed by fluconazole (NCT02136030, ClinicalTrials.gov).
In summary, the lipid formulations of AMB represent a significant step forward in the treatment of invasive fungal infections allowing clinicians to treat for longer periods and with higher doses of AMB due to their relative nephrotoxic-sparing effects when compared with AMBd. The lipid formulations of AMB are used interchangeably by many clinicians although they need to be cautious when making these extrapolations since there may be significant differences in efficacy and/or drug-associated toxicity between AMB lipid formulations as demonstrated in the clinical trial comparing ABLC and AmBisome.46

Leishmaniasis

Leishmaniasis is a protozoan infection transmitted by the bite of a sandfly. Visceral leishmaniasis (VL) is the most severe form of leishmaniasis with 500,000 new cases of VL each year in 70 endemic countries, particularly in the Indian subcontinent, East Africa, South America, and the Mediterranean basin.49 Pentavalent antimonials have been the standard first-line medicines for VL (WHO website; URL: https://globalhealthtrials.tghn.org/site_media/media/articles/WHOs_Technical_Report_Series_-_Control_of_the_Leishmaniases.pdf), but resistance to pentavalent antimonials has been increasing, with cure rates progressively declining to 36%.12,50,51 Thus, alternative drugs have been evaluated for VL, including AMBd and AMB lipid formulations.

Clinical trials evaluating AMBd and lipid-associated formulations of AMB, including AmBisome,4 ABLC,5,6 and AMB in fat emulsion7,8 show that the formulations differ in their levels of efficacy and tolerability profiles. The optimum dosage and duration of AMB treatment required to eradicate Leishmania parasites also varies according to the formulation. The ranges of dosage and duration of AMB treatment to achieve a final cure rate of >90% are shown in Figure 1.4,5,6,7

The efficacy and tolerability of AMB liposomal formulations for VL are the most well established for AmBisome. Data from RCTs show that AmBisome achieves cure rates of >90% after 1 to 5 days of dosing with 7.5 mg/kg or 10 mg/kg, with long-term follow-up of almost 10,000 patients.50,52,53 As shown in Table 4, available data on the efficacy and tolerance of the various other AMB liposomal formulations are from preliminary clinical studies involving small numbers of patients. In the pilot Fungisome study, the definitive cure rates at 6 months were 3/5 (60%) and 5/10 (50%) with a single dose of 5 mg/kg and 7.5 mg/kg, respectively, and 9/10 (90%) after treatment with 2 doses of 5 mg/kg.29,30

More recently, a phase II Fungisome clinical trial was performed to determine if a higher dose regimen (10 mg/kg for cohort I or 15 mg/kg for cohort II) would improve the long lasting cure rate for VL.54 Assessable patients with parasitologically confirmed VL included 28 patients in cohort I and 22 patients in cohort II. All patients were premedicated

Table 4. Clinical experience with liposomal amphotericin B formulations in visceral leishmaniasis.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmBisome</td>
<td>&gt;10,000 patients included in controlled trials, or prospective or retrospective cohorts</td>
</tr>
<tr>
<td>Fungisome</td>
<td>&lt;150 patients in noncontrolled trials</td>
</tr>
<tr>
<td>Ambilip, Amfitas, Amfocan, Amfocare, Amfy</td>
<td>No clinical data yet reported in the PubMed database (NCBI)</td>
</tr>
</tbody>
</table>
with paracetamol and pheniramine maleate although 90% of the patients still experienced infusion-related chills and rigor. Dose limiting toxicities were rare with only 13.3% in cohort I and 6.7% in cohort II, although the authors stated that the actual spectrum of adverse events can only be evaluated using a larger sample size. Efficacy was 100% after infusion of the drug, with a definitive cure of 93.3% in both cohorts at the 6 month follow-up. The investigators concluded that although the drug appears to be safe and efficacious as a high single dose treatment for VL, the requirement to sonicate Fungisome before drug administration needs to be eliminated if it is to be used at the primary health center level since it would be difficult to perform this step at those locations.54,55

Due to the absence of adequate data on the VL efficacy of generic formulations, their use for treatment of VL remains controversial.51 Thus, the WHO only recommends the use of AMBd or AmBisome for VL, with AmBisome recommended as the first-line VL treatment caused by *Leishmania donovani* in Bangladesh, Bhutan, India, and Nepal (WHO website; URL: https://globalhealthtrials.tghn.org/site_media/media/articles/WHO%20s_Technical_Report_Series_-_Control_of_the_Leishmaniases.pdf).

Conclusions
Given the differences in toxicity and efficacy between the different AMB lipid products and the impact these differences can have on quality of care and patient safety, there is a need to distinguish between these products in both the published literature and in clinical use. To address this issue, the US Food and Drug Administration (FDA) published their first draft “Guidance for industry on liposome drug products” in August 2002, and this draft is still under review [FDA website; URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070570.pdf]. In 2013, the European Medicines Authority (EMA) guidelines stated that a liposomal formulation must show equivalence to the innovator product in terms of pharmaceutical quality, nonclinical pharmacokinetics and pharmacodynamics, and clinical pharmacokinetics [European Medicines Agency website; URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500140351.pdf]. This approach at the regulatory level is needed to assure clinicians and patients that they are receiving an effective and safe drug.

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J-PG has been a consultant for Gilead Sciences, Inc.

PGP is a consultant and receives research grant funding from Gilead, Merck, Astellas, Sycnexit, Viamet, and T2 Biosystems.

NCT01652859. Phase I An bioequivalence study to compare two 2 mg/ml liposomal amphotericin B injections in healthy subjects (Clinical Trial). ClinicalTrials.gov.

NCT02136030. Phase II A randomized study to evaluate the safety and efficacy of liposomal amphotericin B and amphotericin B deoxycholate with or without fluconazole followed by flucytosine for the treatment of Cryptococcal Meningitis (Clinical Trial). ClinicalTrials.gov

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