Development of a Novel Oral Amphotericin B Formulation (iCo-019) to treat systemic fungal and parasitic infections.

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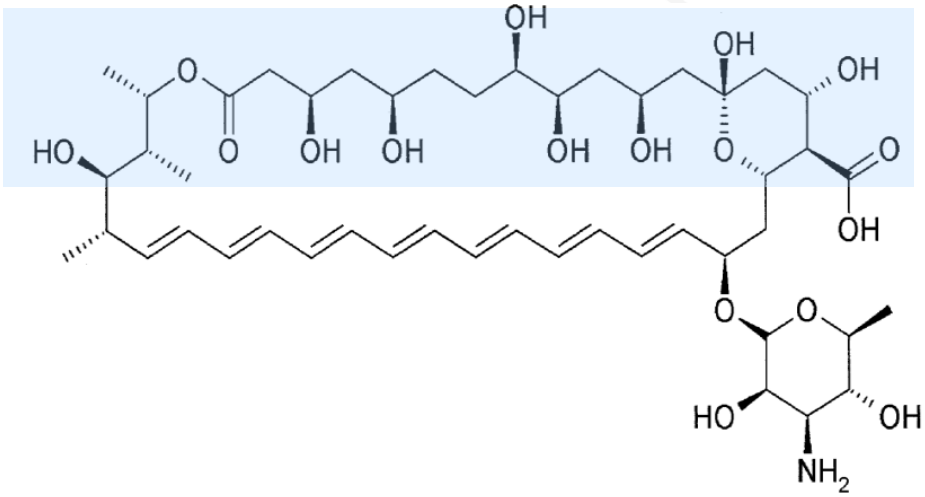
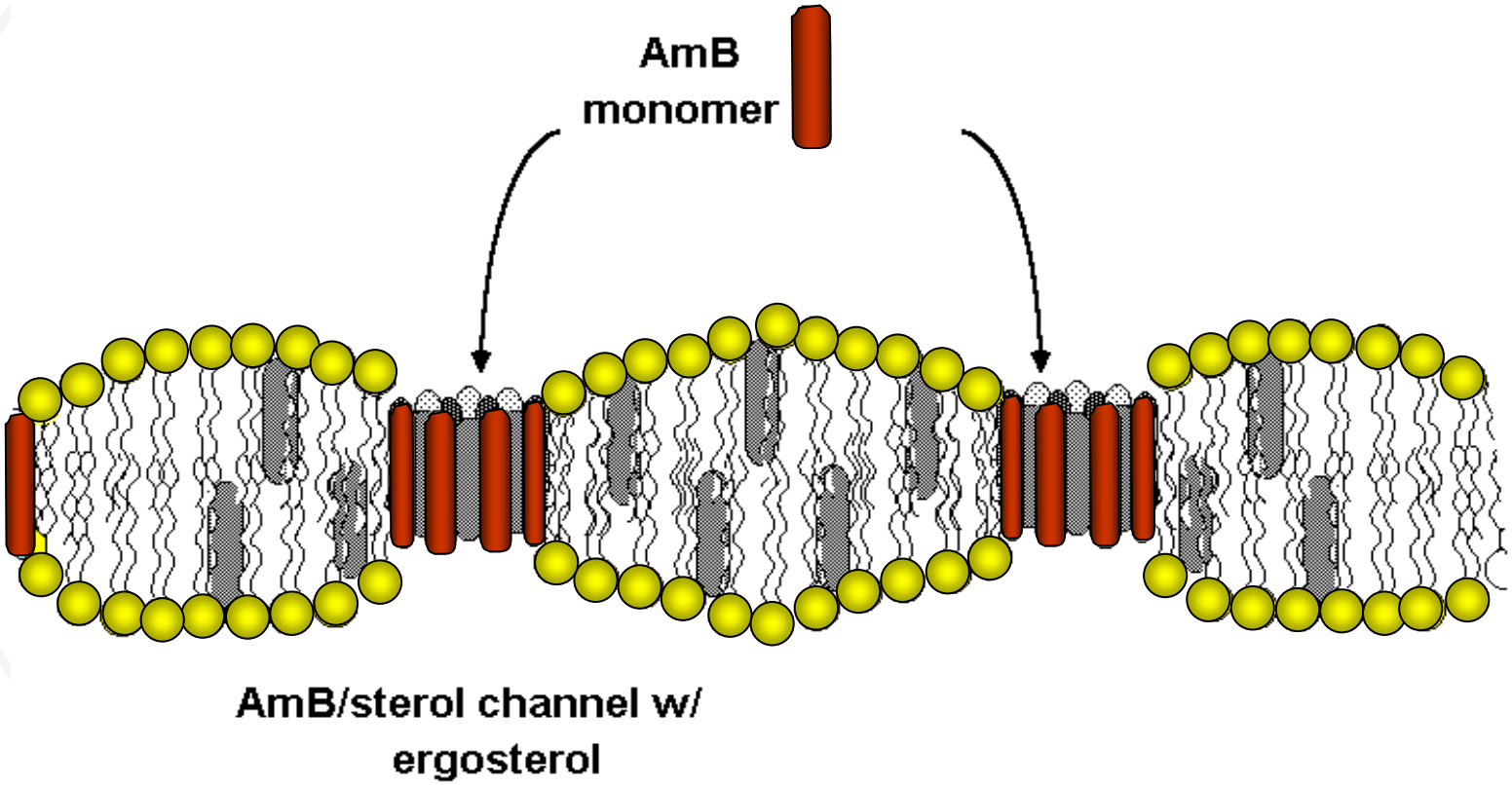
Amphotericin B – The Molecule



- A polyene antifungal agent, first isolated from *Streptomyces nodosus* *(Gold et al., 1955)*
- Amphoteric compound composed of:
  - a hydrophilic polyhydroxyl chain along one side
  - a lipophilic polyene hydrocarbon chain on the other.
- Poorly soluble in water

Amphotericin B Mechanism of Action



Hartsel, Bauer, Kwong and Wasan. Pharm. Res., 2001

Other Potential Indications: Immunocompromised complications, HIV and neglected diseases

Azoles-Resistant Candida infections

Candida species are responsible for a majority of superficial and disseminated fungal infections in humans

Recurrent Vulvovalginal Candidiasis (RVVC), usually defined as four or more episodes of symptomatic VVC within 1 year, affects >9% of women

- Some genes may be associated with Candida albicans resistance to azoles. Pir1 gene is described as responsible to induce resistance in C. albicans

Oropharyngeal Candidiasis (OPC) – often associated with HIV

- *C. albicans*, depends on previous fluconazole treatment and prior OPC infections;
- Recommended azole treatment: 7-14 days
- Can use Amphotericin B i.v. daily as a salvage therapy if oral Amphotericin B does not show expected efficacy
- Relatively common – numbers may favour Phase II study using oral Amphotericin B

Other Potential Indications: Immunocompromised complications, HIV and neglected diseases

Histoplasmosis in patients with concurrent tuberculosis

- Coinfection with tuberculosis in some countries occurs in 8–15% of human immunodeficiency virus (HIV)-infected patients who have histoplasmosis
- Occurs mostly in India, Latin America, etc.
- Difficult treatment due to drug interactions
- Oral Amp B may be beneficial with less drug resistance (prof. Denning)

Fungal Endophthalmitis

- Endogenous fungal endophthalmitis represents intraocular dissemination of a systemic fungal infection
- Among the different fungal species, Candida species is the most common cause of infection, followed by Aspergillus species and cryptococcus
- Hospitalized patients with candidemia reveal that 9-37% of patients developed candidal endophthalmitis
- In India, fungi were isolated in 22% of culture-proven endophthalmitis
- Systemic amphotericin has been the treatment of choice because of its broad-spectrum coverage

Other Potential Indications: Immunocompromised complications, HIV and neglected diseases

Febrile Neutropenia

- Use fluconazole as a control with a salvage therapy available
- Treatment duration: treat until 2-3 days after patient is asymptomatic (will be specified)

Chronic Refractory Mucocutaneus Candidiasis (CMC)

- Persistent or recurrent candidal infection due to inherited T-cell defects
- Typically, only poorly controlled with anti-fungals (azoles)
- Potential for a better improvement with chronic oral Amphotericin B therapy – less resistance, less drug interaction, safe

Visceral Leishaniasis (VL)

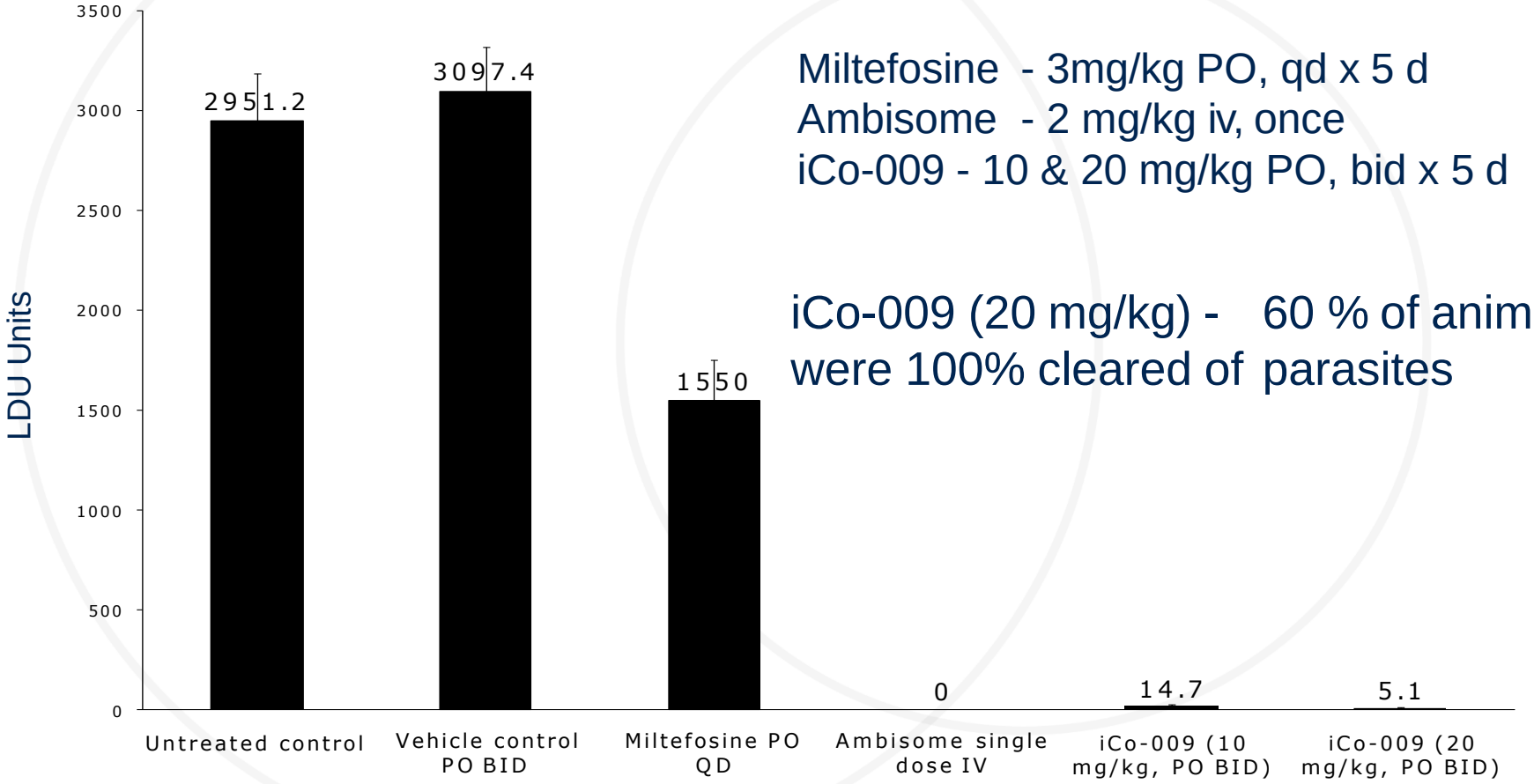
- Parasitic infection common in tropical, subtropical regions as well as Southern EU
- If untreated almost always causes death
- Amphotericin B IV is a standard treatment which is expensive, not tropically stable and difficult to administer
- Miltefosine is the first oral treatment, with numerous side-effects

Opportunities to increase accessibility

Most effective treatment is parenteral amphotericin B resulting in:	Oral amphotericin B overcoming barriers to treatment:
1. Loss of income due to hospitalization for IV therapy	1. Easy to administer/at home administration
2. High cost of administration	2. Decreased cost of administration
3. Risk of infusion-related side effects	3. Lack of Infusion-related side effects (i.e. fever, chills etc.)
4. Risk of systemic toxicity	4. Lack of kidney, liver and GI toxicity
5. Limited accessibility	5. Increased accessibility
6. Not heat stable	6. Thermal stability at tropical temperatures

VL & Anti-Fungal Studies

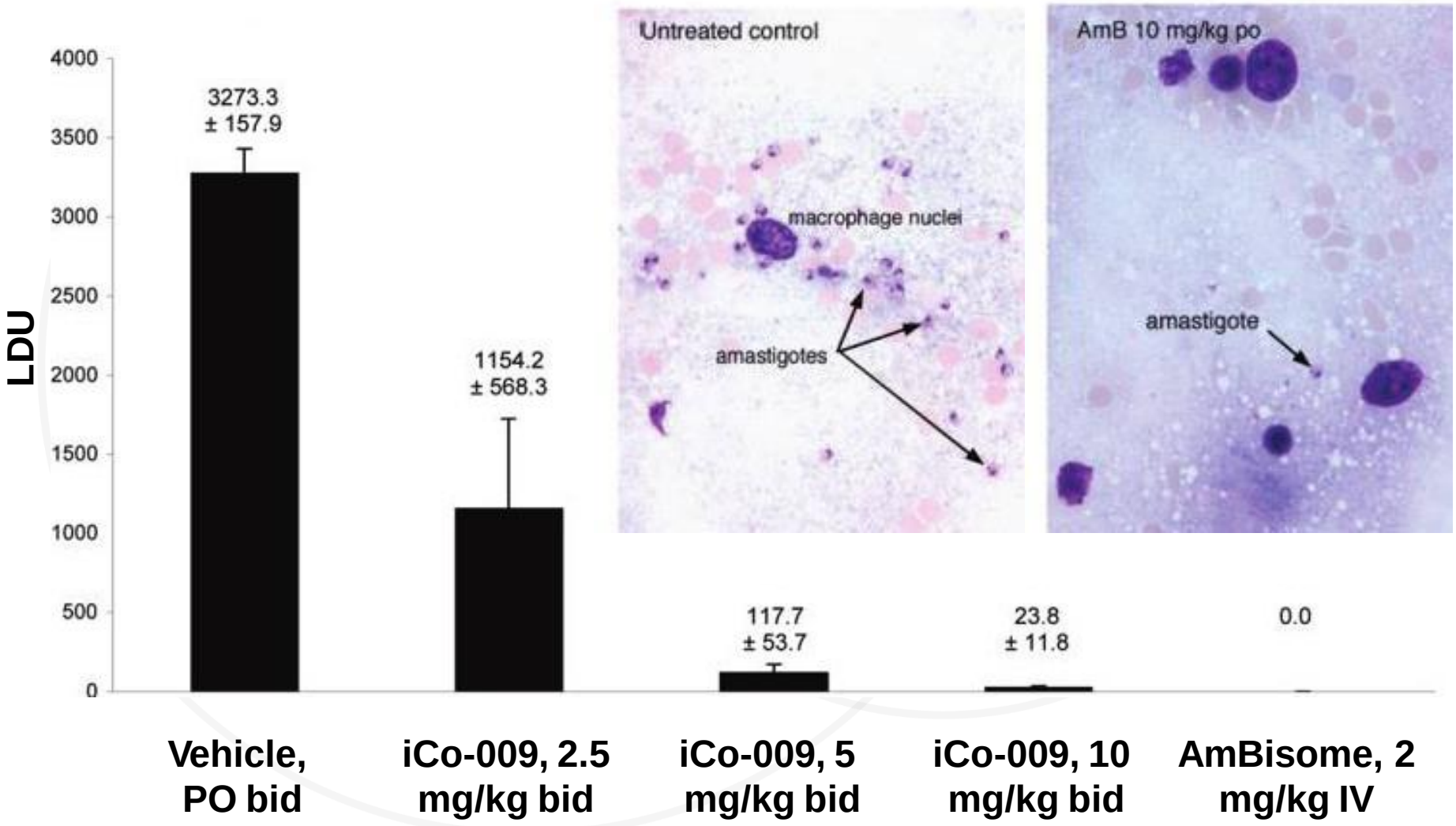
iCo-009 Highly Effective
Eradicates Parasite in Mouse Model of VL
Independent Lab Funded by Gates Fdn.



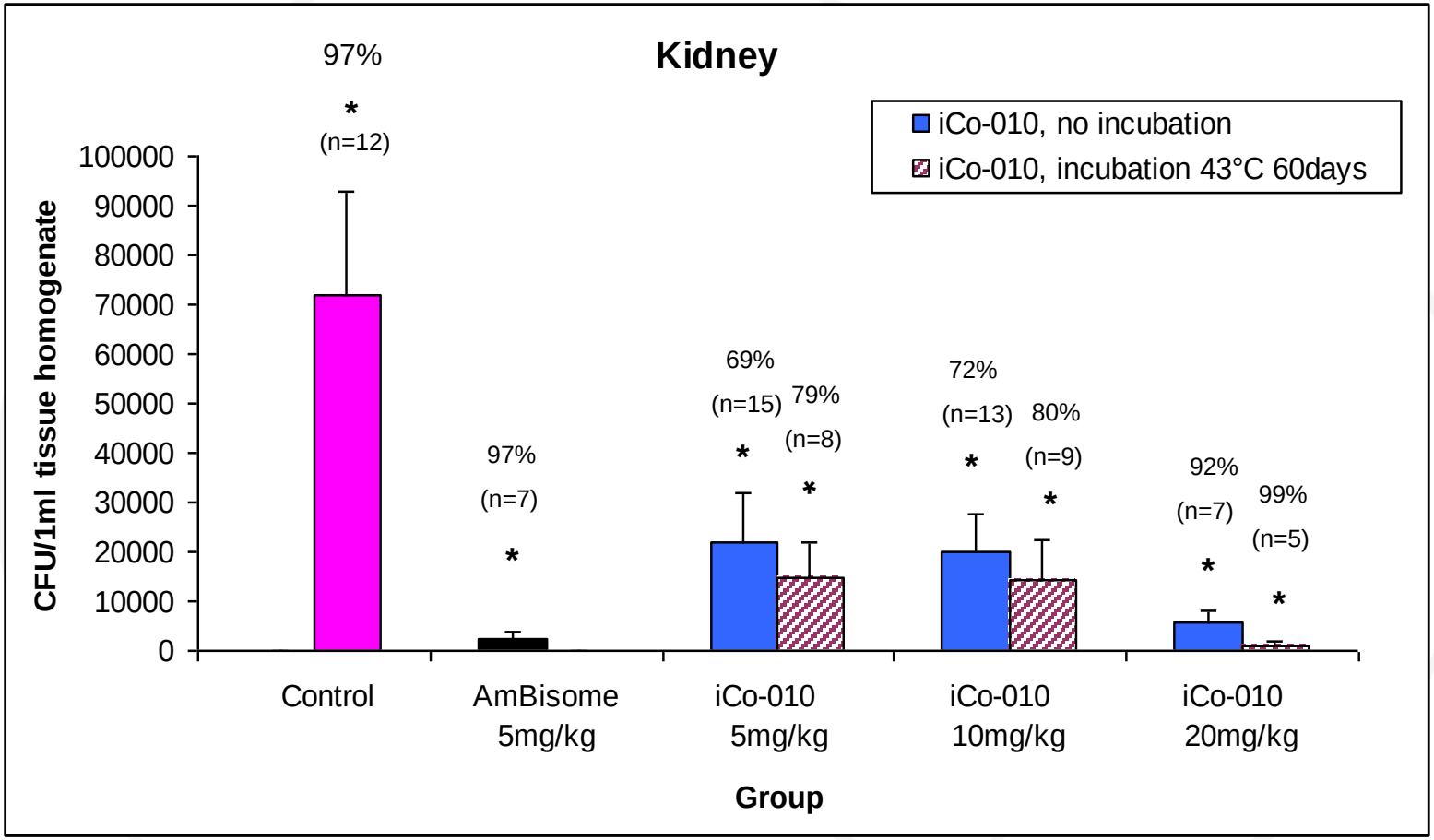
Miltefosine - 3mg/kg PO, qd x 5 d
Ambisome - 2 mg/kg iv, once
iCo-009 - 10 & 20 mg/kg PO, bid x 5 d

iCo-009 (20 mg/kg) - 60 % of animals were 100% cleared of parasites

iCo-009 ED_{50} in Mouse VL Model < 2.5 mg/kg



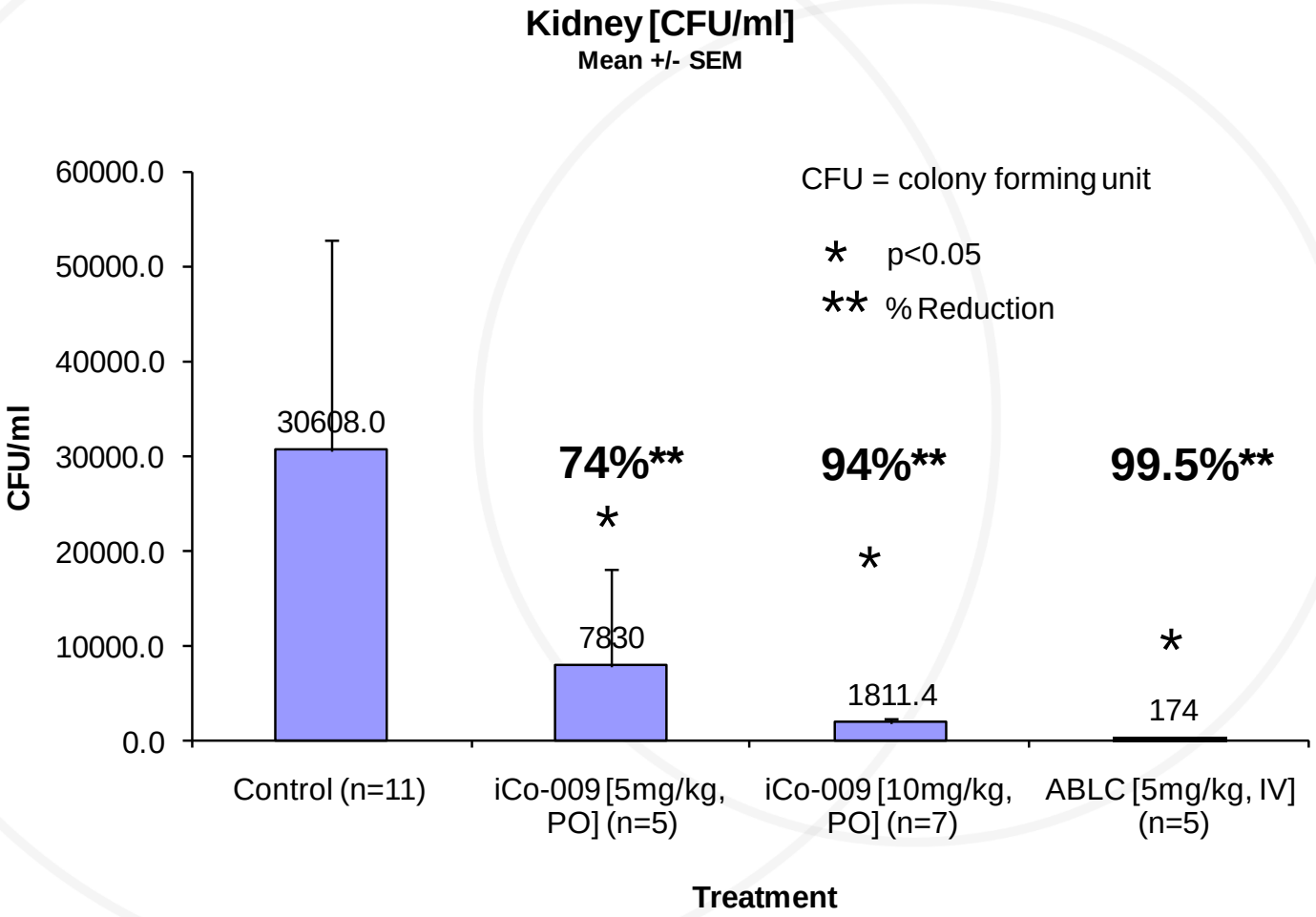
Comparison of the Efficacy of Oral Amp B and Ambisome in the mouse model



Comparison of the efficacy of oral AmB at 5, 10 and 20mg/kg in the lipid-based iCo-010 formulation (non incubated and incubated at 43° C for 60 days) and AmBisome, 5mg/kg, IV, once in the kidneys of a mouse model of invasive candidiasis. Animals were infected and allowed to establish the infection over two days. The animals were treated for the next five consecutive days once daily and sacrificed 7 days following the completion of the treatment. Organs were harvested and homogenized to count CFU of the fungus/1ml of the homogenate (Mean CFU count ±SEM).

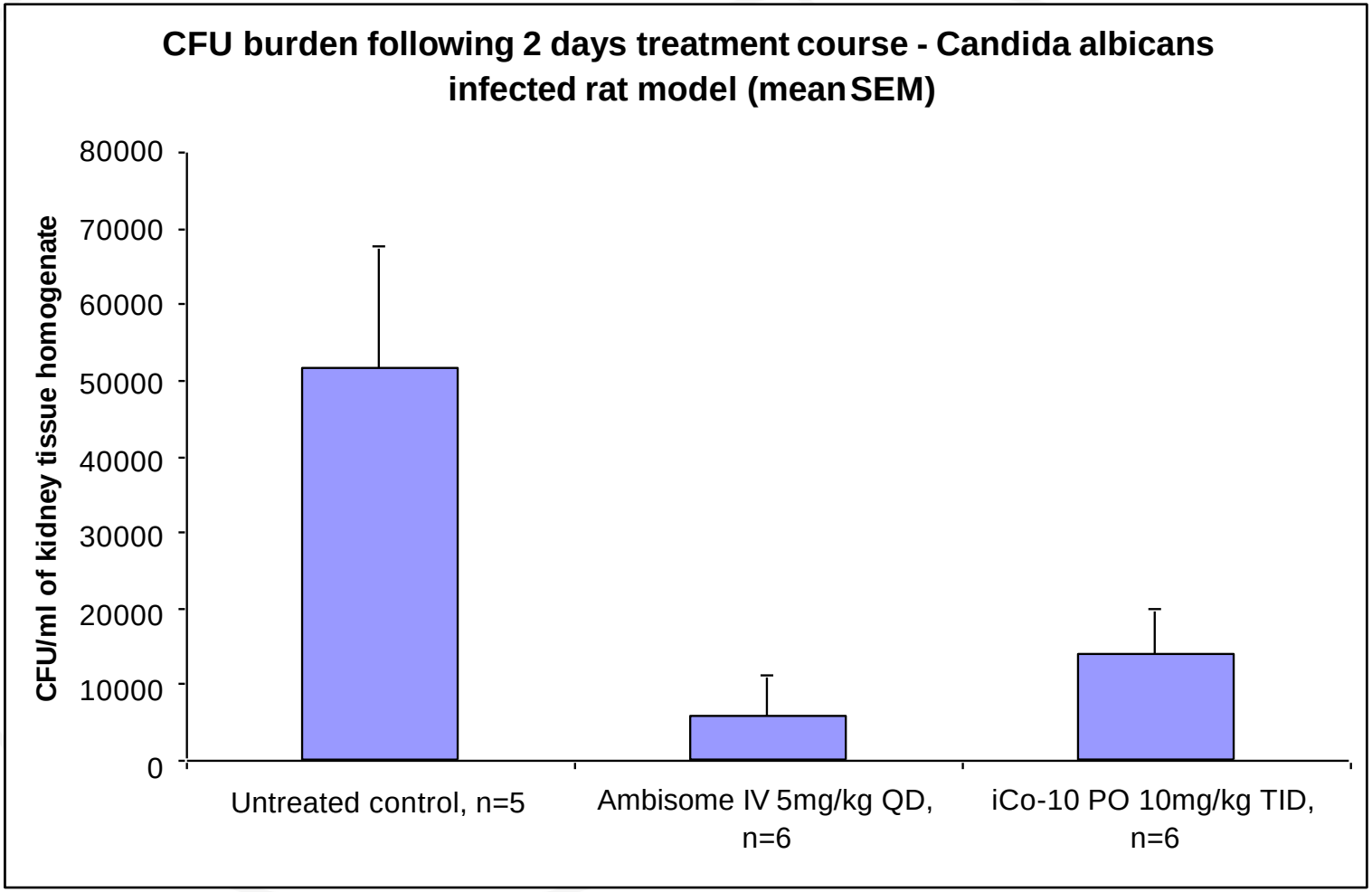
* significantly different from the untreated control group

iCo-009 Demonstrated Significant Anti-fungal Activity in Rat Model of *Candida albicans*



No kidney toxicity as measured by plasma creatinine levels

iCo-010 Demonstrated Significant Anti-fungal Activity in a Rat Model of *Candida albicans*

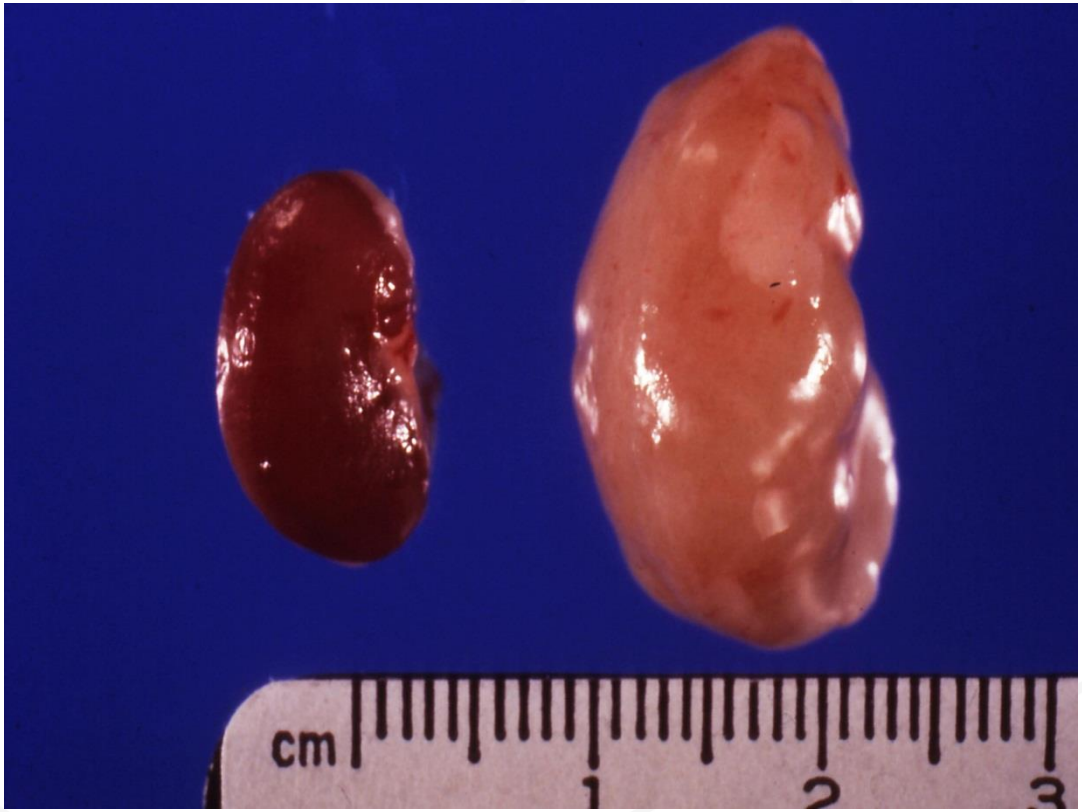


Biodistribution of amphotericin B in mice following multiple dose oral treatment with iCo-010

	iCo-010 20mg/kg BID for 5 days, n=7	iCo-010 10mg/kg BID for 5 days, n=6	iCo-010 5mg/kg BID for 5 days, n=6	iCo-010 2.5mg/kg BID for 5 days, n=6	Fungizone® 2mg/kg QD for 5 days, n=6
Plasma	538 ± 27	418 ± 48	232 ± 22	172 ± 10	791 ± 90
Liver	3494 ± 287	2543 ± 510	836 ± 97	446 ± 44	49794 ± 6993
Spleen	1939 ± 87	1407 ± 120	916 ± 121	342 ± 20	27008 ± 2400
Lung	3179 ± 312	2014 ± 185	1168 ± 307	408 ± 47	7533 ± 1299
Kidney	3685 ± 334	2268 ± 220	813 ± 89	495 ± 31	9100 ± 1140
Heart	366 ± 31	338 ± 41	156 ± 10	84 ± 8	1139 ± 243
Brain	169 ± 6	157 ± 3	112 ± 10	59 ± 5	234 ± 23
Skin	393 ± 45	165 ± 19	116 ± 20	BLQ	420 ± 269
Muscle	26 ± 16	24 ± 8	BLQ	BLQ	468 ± 148
Visceral Fat	2114 ± 512	904 ± 220	471 ± 112	BLQ	3324 ± 654

Antifungal Activity-Efficacy correlated to AUC and Biodistribution

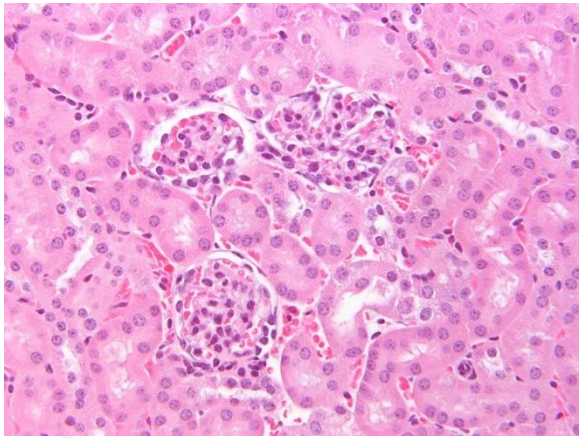
Preliminary evidence shows efficacy against Candidiasis kidney gross morphology of an untreated and treated rat



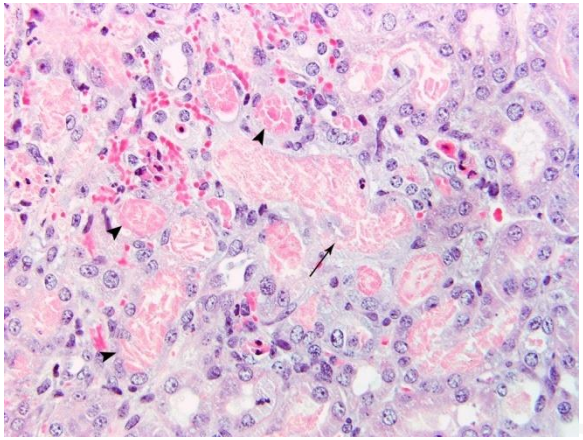
Assessment of kidney, liver and jejunum toxicity of iCo-010 compared to multiple dose Fungizone® IV

Kidney

Oral AmB 20mg/kg BID for 5 days

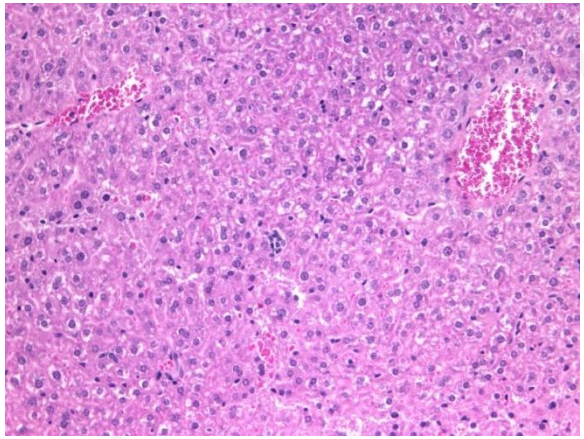


IV Fungizone 2mg/kg QD for 5 days

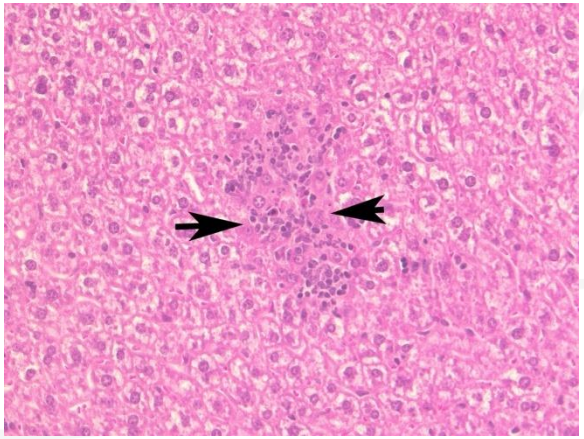


Liver

Oral AmB 20mg/kg BID for 5 days

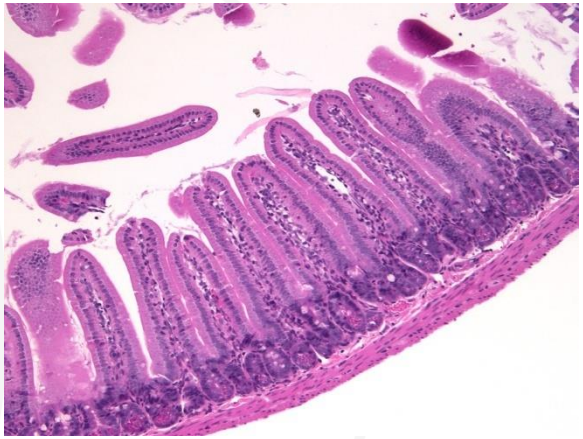


IV Fungizone 2mg/kg QD for 5 days

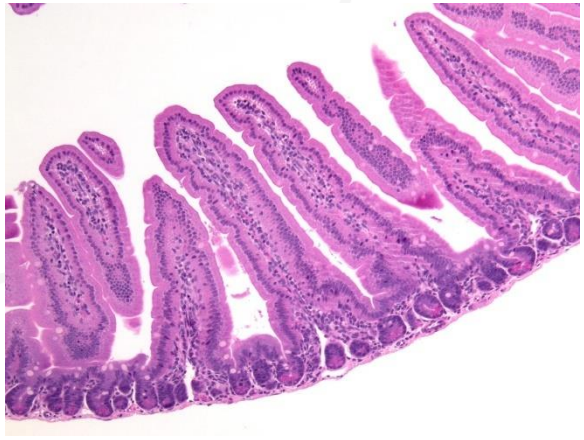


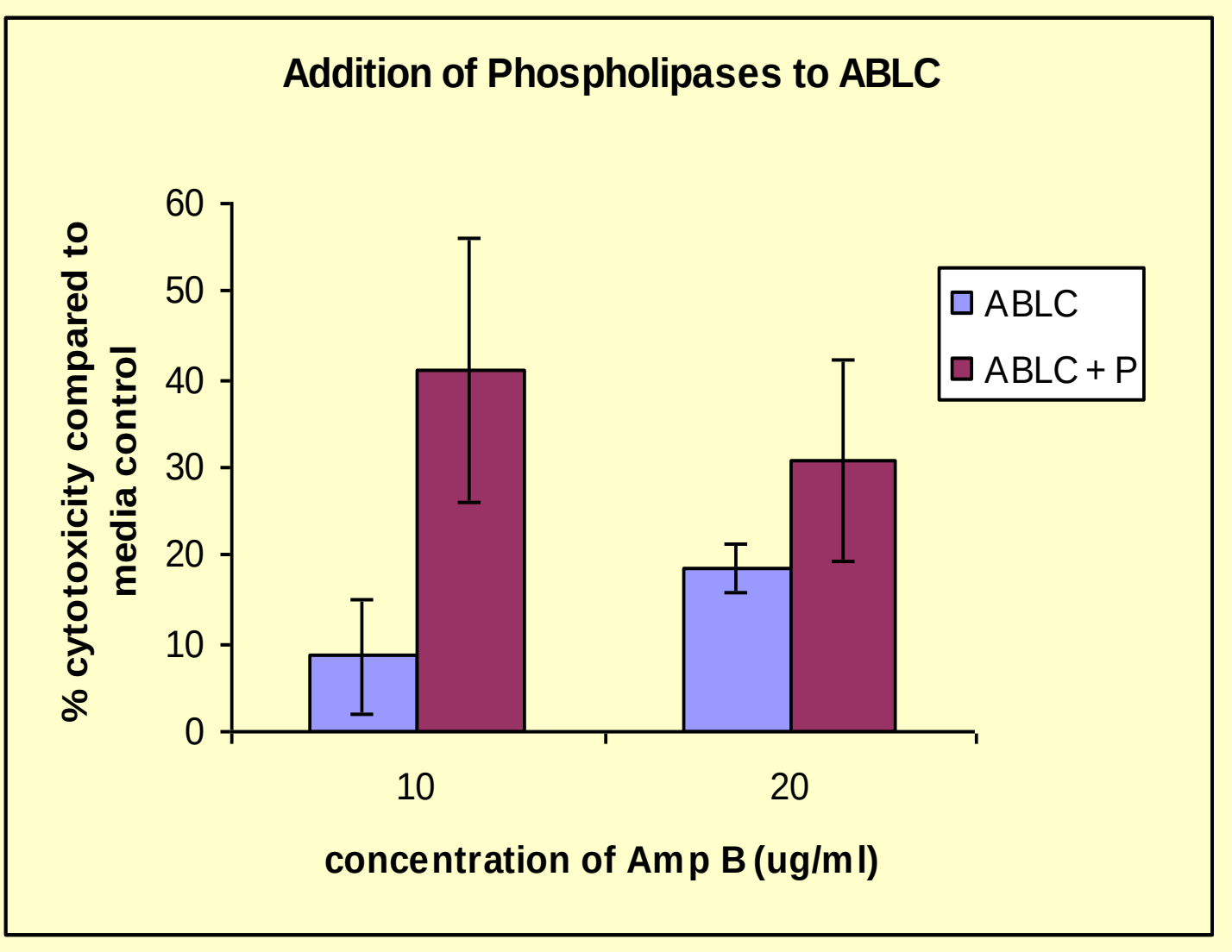
Jejunum

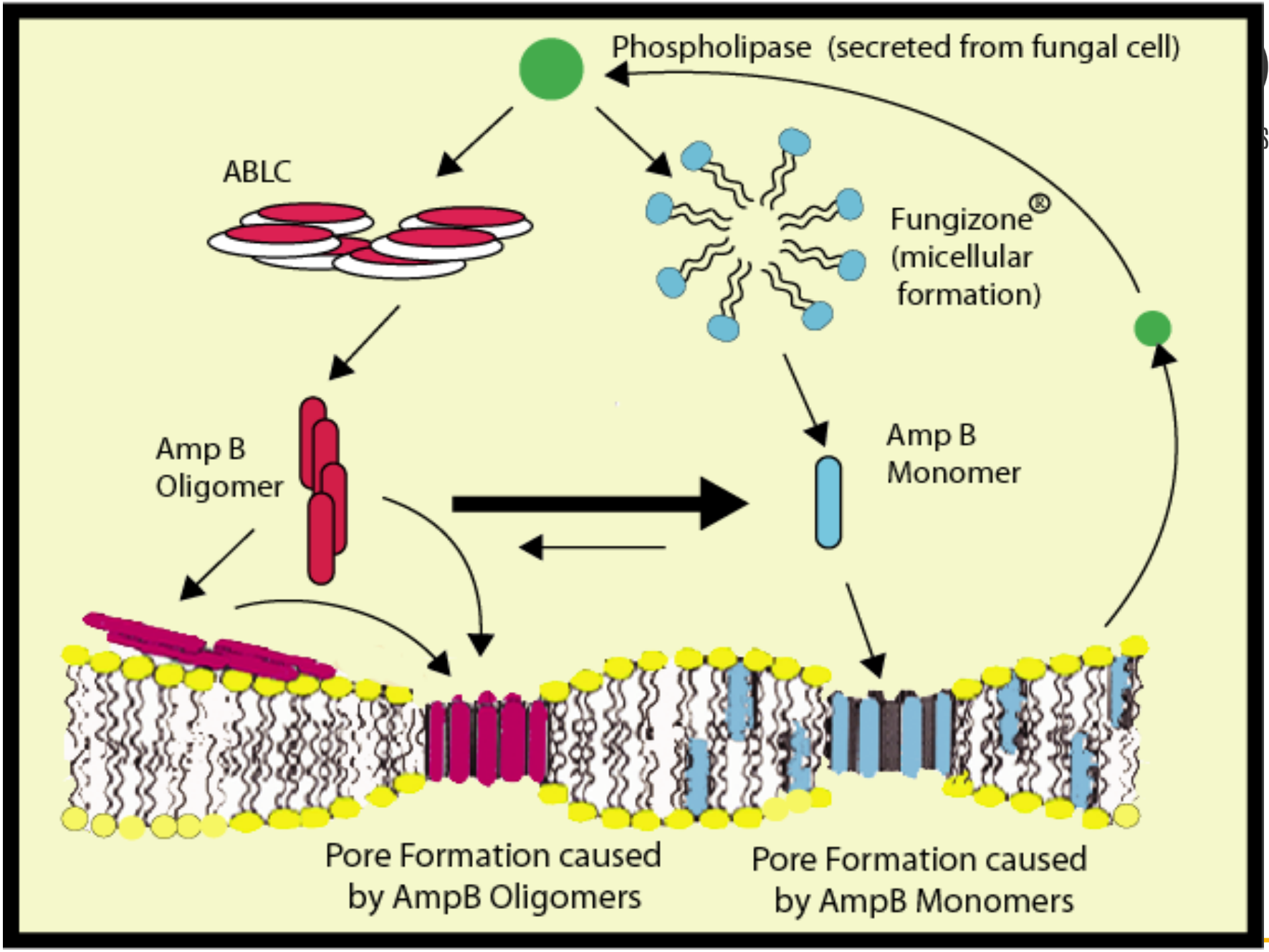
Oral AmB 20mg/kg BID for 5 days



IV Fungizone 2mg/kg QD for 5 days

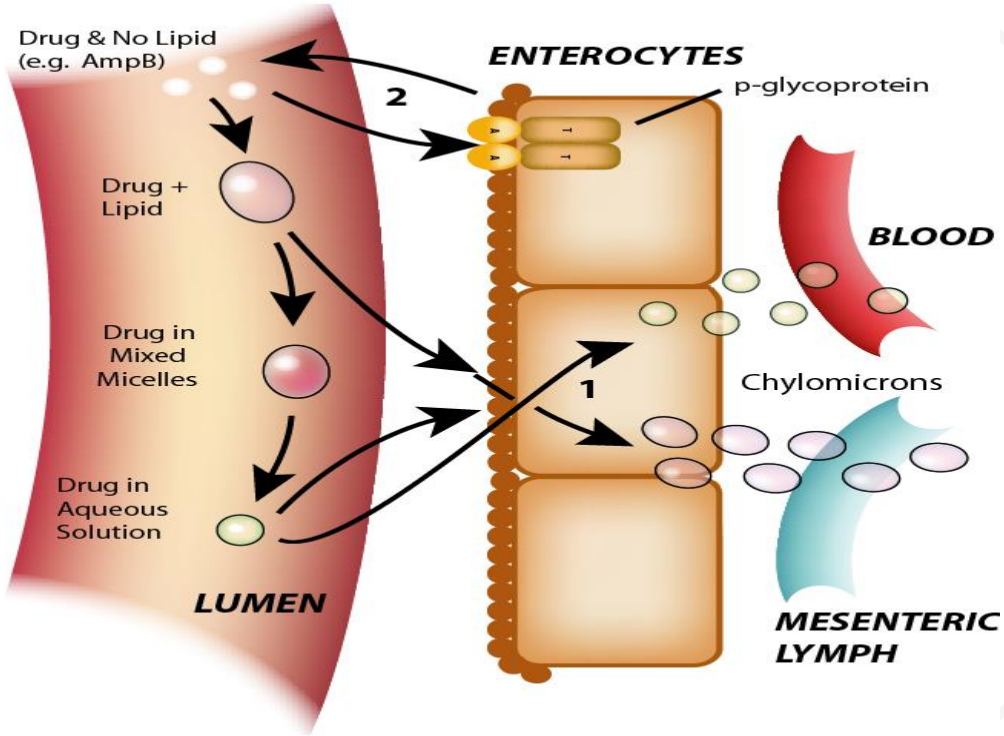



Addition of Phospholipases to ABLC
% cytotoxicity compared to media control
60
50
40
30
20
10
0
10
20
concentration of Amp B (ug/ml)
ABLC
ABLC + P


Phospholipase (secreted from fungal cell)
ABLC
Fungizone®
(micellular
formation)
Amp B
Oligomer
Amp B
Monomer
Pore Formation caused
by AmpB Oligomers
Pore Formation caused
by AmpB Monomers

Lymphatic Transport

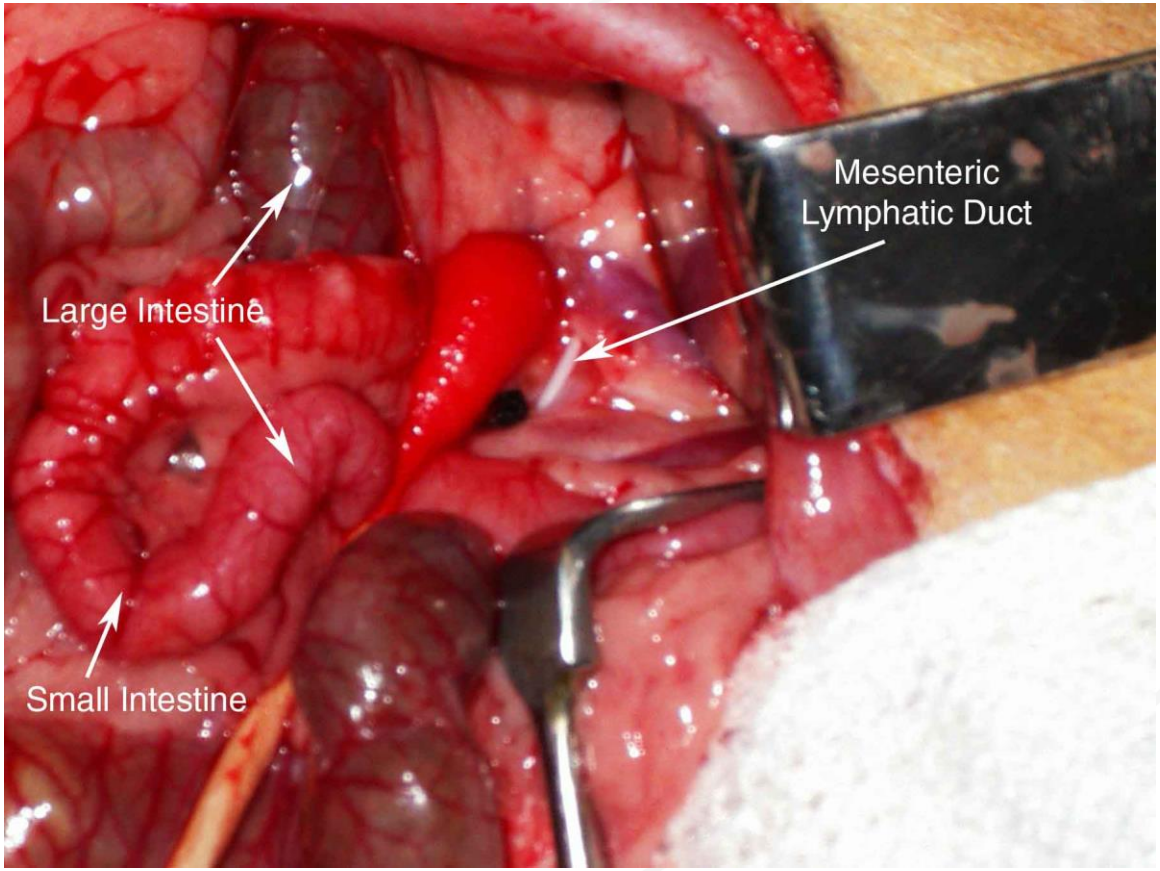
Figure 1.



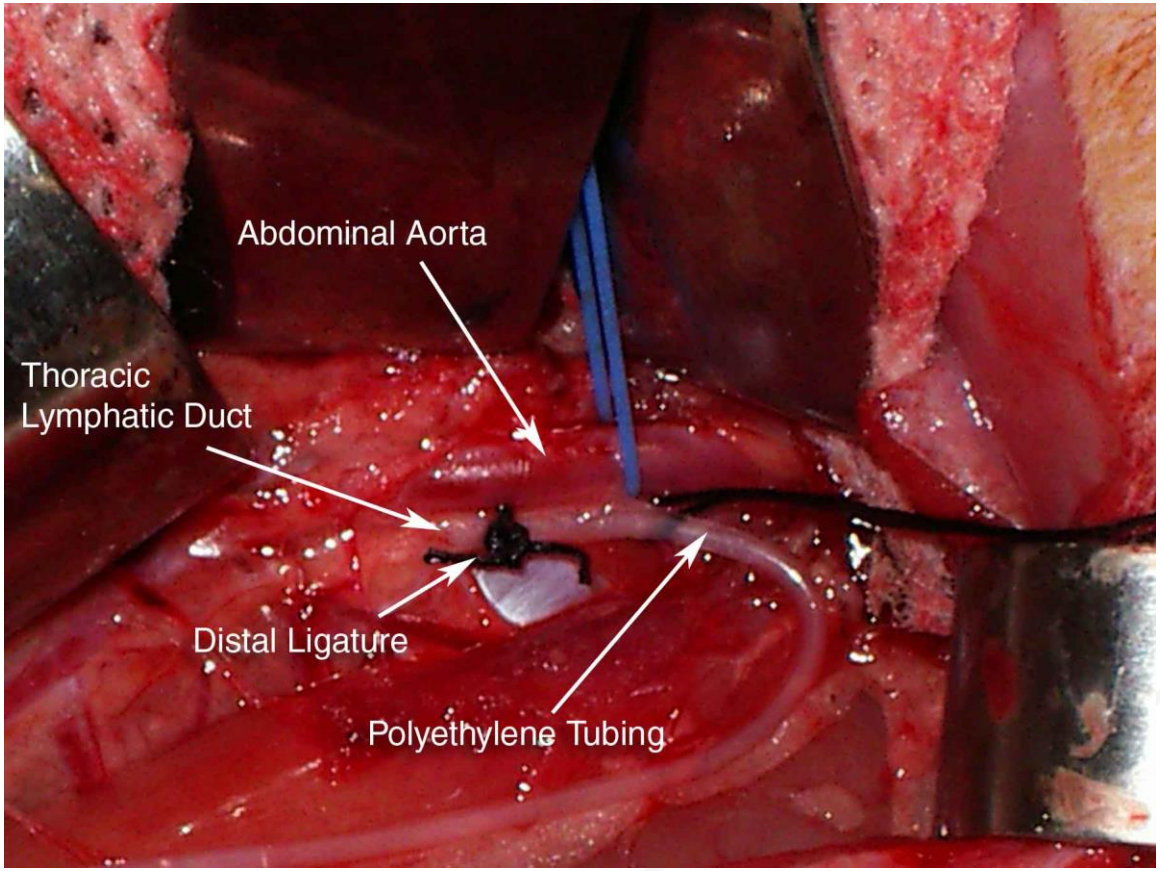
1 Hypothesis: Drug associated with lipid is targeted to the Mesenteric Lymph.

2 Alternative Hypothesis: Drug associated with lipid inhibits drug efflux by p-glycoprotein.

Mesenteric Lymph Duct



Thoracic Lymph Duct



Lymphatic Transport of AmpB

Effect of Peceol® on the Lymphatic Transport through the mesenteric lymph duct of Amphotericin B in Rats following a 5 mg/kg Oral Gavage Dose of Amphotericin B.

	Amount (mg) of Amphotericin B transported lymphatically by time interval			Total lymph output (ml)
Formulation	0-4h	4-6h	6-8h	0-8h
Suspension (n=6)	25.4 ± 6.4	14.0 ± 2.3	5.2 ± 0.9	30.5 ± 5.6
Peceol® (n=6)	51.4 ± 24.5	38.2 ± 18.5*	64.4 ± 27.5*	19.4 ± 5.9

*$p<0.05$ vs. suspension formulation using normal scores ranks. Amphotericin B Suspension is Fungizone® and Amphotericin B in Peceol® is the drug dissolved in 100% Peceol. Data reported as mean +/- standard error of the mean.

Summary

Potential Mechanisms for lack of renal toxicity and enhanced drug absorption

- Drug delivery package makes AmpB primarily available for fungal cells (fungal phospholipases)
- Lymphatic transport/increased bile acid secretion
- Enhanced drug solubility
- Enhanced stability at gastric pH

Original Oral Amp B Formulations demonstrated good safety profile and excellent efficacy

Formul'n	Model	Indication	Dose	Efficacy	Toxicity
iCo-009	Mouse	Visceral leishmaniasis	10 and 20mg/kg BID x 5d	Parasite eradicated (up to 99%)	Creatinine levels normal
iCo-009	Rat	Aspergillus fumigatus	10mg/kg PO BID	Plasma galactomannan levels reduced by 80% at 48 hr; Significant reduction in colony forming units	No kidney toxicity as evidenced by plasma creatinine levels
iCo-009	Rat	Candida albicans	5 or 10mg/kg PO BID x 3d	Significant reduction in colony forming units	No kidney toxicity as evidenced by plasma creatinine levels
iCo-010	Rat	Candida albicans	10mg/kg TID x 3d	Significant reduction in colony forming units	No kidney toxicity as evidenced by plasma creatinine levels
iCo-010	Mouse	Visceral leishmaniasis	2.5, 5, 10 and 20mg/kg BID	Comparable to iCo-009	Comparable to iCo-009
iCo-010	Mouse	Biodistribution & Toxicity	20mg/kg BID x 5d 10mg/kg BID x 5d 5mg/kg BID x 5d 2.5mg/kg BID x 5d	Significant reduction in colony forming units	Comparable to iCo-009 (no liver, kidney or GI toxicity by enzymatic and histopathology)

Presentation of Different Formulations

Oral Amphotericin B Formulations

iCo-019 chosen for good pK, drug adherence, ease of manufacturing, and reproducibility of capsules

- "Pharmacokinetics and tissue distribution of amphotericin B following oral administration of three lipid-based formulations to rats". Drug Development and Industrial Pharmacy 2013, 39(9): 1277-1283
  - iCo-009, iCo-010, iCo-011 studied
  - Conclusion: "Pharmacokinetics of iCo-010 is more favourable than those of iCo-011 and iCo-009 for the advantage of higher tissue exposure and prolonged MRT".
- Additional development of solid oral formulations of amphotericin B (new derivatives, new IP filings)

Summary of Main Pharmacokinetic Parameters in Beagles

Formulation		C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}Tlast}$ (ng*hr/mL)	MRT_{Last} (hr)
iCo-010	Mean	57.4	8.0	2879	31.7
	SE	2.6	2.3	128	0.4
iCo-019	Mean	46.4	14.0	1700	26.7
	SE	7.1	4.5	291	0.6
iCo-022	Mean	52.5	8.3	2146	27.3
	SE	7.2	3.3	369	1.8

Oral Amphotericin B Formulations

Bridging Derivatives: in Beagles

- "The lack of a significant difference between the pharmacokinetic parameters presented for the three formulations suggests that each is capable of delivering similar levels of amphotericin B into the plasma.
- Furthermore, the plasma levels of amphotericin B 24 hrs following repeated doses of iCo-019 and iCo-022 were similar at 56.0 ± 6.9 ng/mL and 52.3 ± 4.6 ng/mL, respectively an indication that these two formulations could deliver similar levels of amphotericin B into the plasma"
- "The levels observed in some of the tissues in this study are similar to range of tissue concentrations of amphotericin B, 45 – 495 ng/g tissue observed seven days following oral dosing in mice, tissue concentrations that were effective in producing a 69-96% reduction of fungal burden in a mouse model of systemic candidiasis."*

Hnik P, Wasan EK, Wasan KM, ASSESSING THE PHARMACOKINETICS AND BIODISTRIBUTION OF AMPHOTERICIN B FOLLOWING ORAL ADMINISTRATION OF THREE NOVEL ORAL AMPHOTERICIN B FORMULATIONS TO BEAGLE DOGS, Abstract submitted to the 2020 AAPS PharmSci 360 Annual Meeting, October 2020, New Orleans, USA.

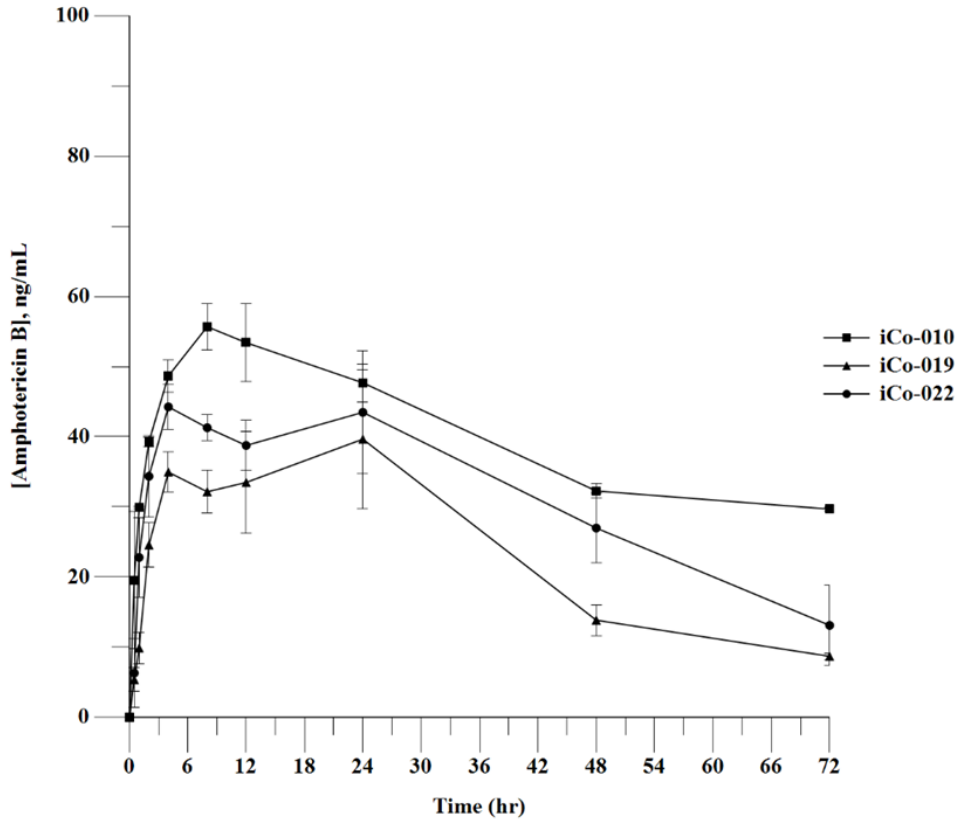
Beagle and Phase I Human Studies

Supporting Non-clinical Studies

- PK work in beagles with several derivatives
- Tissue distribution studies in beagles
- Fed/fasted beagle study
- Non-GLP toxicology in beagles, 7-day dose ranging
- GLP toxicology, in beagles, 14-day dose ranging
- Drug stability work ongoing – 24 months data points available

Beagle PK Studies: iCo-019 demonstrates PK profile similar to iCo-010

Mean Plasma Levels of Amphotericin B Following Oral Dosing With 100 mg of Three Different Formulations



Beagle Toxicology Summary: No observed toxicity

- Biodistribution study in Beagles: N=15
  - Original formulation: N=3
  - Two derivative formulations: N=12, (one of which moved into further studies)
  - No observed toxicity, comparable PK data between derivatives
- PK/Tissue distribution fed-fasted (dose escalation) in Beagles: N=4 (M)
  - No observed toxicity, 500mg dose (5 X 100 mg capsules)
- 7-day Non-GLP in Beagles: N=16
  - No observed toxicity, BID dosing, doses up to 1000 mg
- 14-day GLP in Beagles: N=38
  - No observed toxicity, doses up to 600 mg

Clinical Phase 1a: Study Design

A Phase 1a, placebo-controlled, single dose ascending study to assess the safety, tolerability, and bioavailability of Oral Amphotericin B in healthy male and non-pregnant female subjects between 18 – 55 years of age.

Objectives:

Primary objective**:**

- To evaluate the safety and tolerability of multiple dose levels of a single oral administration of oral Amphotericin B.

Secondary objective**:**

- To assess the pharmacokinetics and bioavailability of oral Amphotericin B after a single dose oral administration.

Study Design:

- Subjects were randomized into one of four cohorts, each representing an ascending single dose of treatment: 100 mg, 200 mg, 400 mg and 800 mg.
- Each cohort consisted of eight subjects where six subjects were randomized to receive the investigational product and two were randomized to receive the placebo.
- All subjects were followed for seven days after dosing.

Clinical Phase 1a: Study Results

A Phase 1, placebo-controlled, single dose ascending study to assess the safety, tolerability, and bioavailability of Oral Amphotericin B in healthy male and non-pregnant female subjects between 18 – 55 years of age.

Objectives:

Primary objective**:** To evaluate the safety and tolerability of multiple dose levels of a single oral administration of oral Amphotericin B

- Study met its primary endpoint of safety and tolerability
- No serious adverse events nor drug-related adverse events
- No gastro-intestinal (GI) side effects, even at the highest dose of 800 mg
- No indication of kidney or liver toxicity

Secondary objective**:** To assess the pharmacokinetics and bioavailability of oral Amphotericin B after a single dose oral administration

- Secondary endpoint achieved, demonstrating enhanced plasma AUC measures versus direct competition

Summary of Pharmacokinetic Parameters following Single Dose Studies of iCo-019

Phase 1a, iCo-019 in subjects dosed with 100mg to 800 mg Amphotericin B

Dose (mg)	T_{max} (hr) Median (Range)	C_{max} (ng/mL) Median (Range)	$AUC_{0\text{-}TLast}$ (hr * ng/mL) Median (Range)	$T_{1/2}$ (hr) Median (Range)
100	6.0 (6 - 6)	28.0 (22.7-43.6)	759.7 (635.8-1606.4)	27.3 (14.4-55.1)
200	6.0 (6-8)	28.6 (18.8-42.5)	804.0 (596.1-1344.9)	24.6 (15.3-68.8)
400	6.0 (6-10)	28.4 (20.2-41.1)	1089.2 (461.8-1856.8)	39.0 (13.7-142.1)
800	7.0 (6-10)	32.1 (29.9-42.8)	1345.5 (915.1-1854.7)	25.6 (23.1-32.7)

Clinical Phase 1b: Study Design

A Phase 1b, Single-Center, Double-Blind, Randomized Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of 100 mg and 400 mg Oral Amphotericin B (iCo-019) or Placebo Administered for 10 Days in Healthy Subjects

Objectives:

Primary objective**:**

- To evaluate safety and tolerability after repeated administration of 100 mg and 400 mg doses of oral Amphotericin B (iCo-019) for 10 days in healthy subjects

Secondary objective**:**

- To evaluate pharmacokinetic profile after repeated administration of oral Amphotericin B (10 days) in healthy individuals

Study Design:

- Approximately 12 healthy subjects, aged 18-55 years of age, were randomized to one of the two doses of oral Amphotericin B (100 mg or 400 mg) or a Placebo (5 subjects received oral Amphotericn B and one subject received Placebo in each cohort). Subjects were dosed for 10 days and followed for additional 5 days post-treatment.

Clinical Phase 1b: Study Results

A Phase 1b, Single-Center, Double-Blind, Randomized Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of 100 mg and 400 mg Oral Amphotericin B (iCo-019) or Placebo Administered for 10 Days in Healthy Subjects

Objectives:

Primary objective**:** To evaluate safety and tolerability after repeated administration of 100 mg and 400 mg doses of oral Amphotericin B (iCo-019) for 10 days in healthy subjects

Study met its primary endpoint of safety and tolerability

- No serious adverse events nor drug-related toxicity events
- Both repeated drug doses were well tolerated
- No indication of kidney or liver toxicity

Secondary objective**:** To assess the pharmacokinetics and bioavailability of oral Amphotericin B after a single dose oral administration

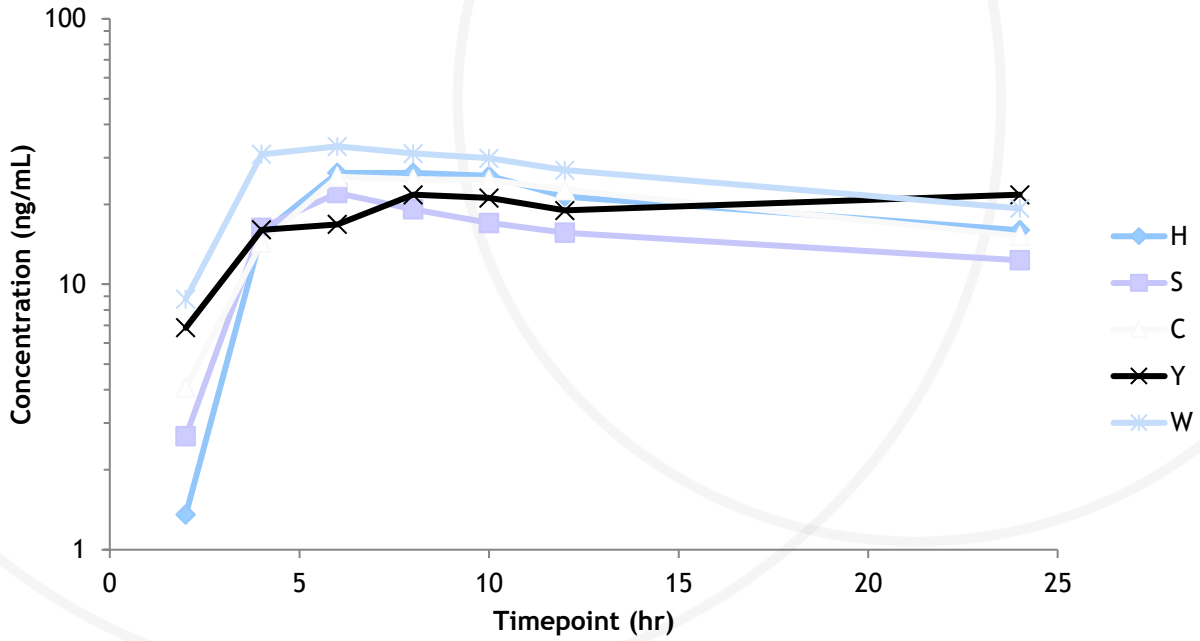
- ICO-019 at the 100 mg dose achieved a median plasma Cmax of 25 ng AmB/mL and AUC (0-inf) 990 hr* ng/mL after day 1 of dosing and a median plasma Cmax of 44 ng AmB/mL and AUC (0-inf) 1998 hr*ng/mL after 10 day of dosing. This approximate doubling of the AUC (0-inf) measure between day 1 and day 10 was observed not only at the 100 mg dose but at the 400 mg dose as well
- Results recently submitted to the American Association of Pharmaceutical Scientists Meeting

Time Course of Mean Plasma Concentration Day 1

100 Mg dose, t=0 to 24hr log-linear plot of mean plasma concentration vs. time.

Overlay of Patients

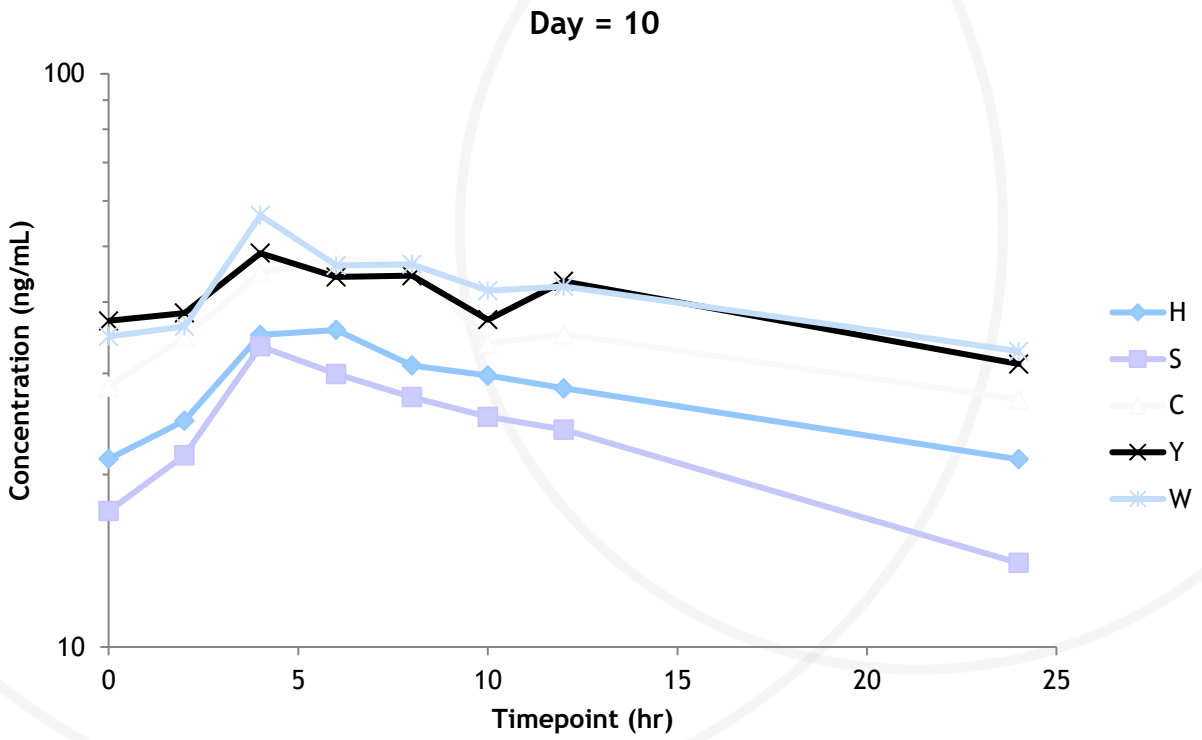
Day = 1



Time Course of Mean Plasma Concentration Day 10

100 Mg Dose, t=0 to 24hr log-linear plot of mean plasma concentration vs. Time.

Overlay of Patients



Summary of Day 1 (t=0 to 24 hrs) and Day 10 (t=0 to 24hrs) Pharmacokinetic Parameters

Phase 1b, iCo-019 in subjects dosed with 100mg of Amphotericin

	Tmax (hr)	Cmax (ng/ml)	AUC0-inf (hr*ng/ml)	T1/2 (hr)
Day 1	9.6 +/- 8.1 (n=5)	25.7 +/- 4.6 (n=5)	990.6 +/- 155.5 (n=4)	24.5 +/- 4.9 (n=4)
Day 10	4.8 +/- 1.1 (n=5)	44.4 +/- 9.7 (n=5)	1997.7 +/- 761.1 (n=5)	31.0 +/- 8.8 (n=5)

Oral Amphotericin B: iCo-019 Formulation Technology

- Formulation designed specifically to overcome the 1) limited absorption of Amphotericin B from the GI tract and 2) toxicology issues for fungal infections
- iCo-019 as Lead based on stability & solubility data
  - 24 month stability data available
- Proprietary blend of mono- and di-glycerides (FDA GRAS approved)
- Low COGS compared to any injectable
  - Easy formulation scale-up
  - Relatively few steps in formulation
  - Affordable lipid excipients

Advantages of iCo-019, Oral Amphotericin B Formulation

- First available Oral Fungicidal Agent (only Fungistatic Agents, Diflucan® from Pfizer) for VVC
  - Treating patients with drug-resistant strains (decrease hospitalization and eliminate IV AmpB Therapy)
- Orphan Drug Designation FDA 2010 for VL
- US Patents Issued 2013 & 2014
- Phase I and 1b Human Clinical Trials Completed 2020
- Easy to store
- Easy to administer

iCo-019: Oral Amphotericin B Product Profile

Product	iCo-019
Class	Anti-fungal/anti-parasitic
Mechanism of Action	Membrane disruption, Immune stimulant properties Lymphatic transport may be involved in absorption
Development Stage	Clinical: IND enabling studies completed, Phase 1 single dose-escalating study completed 2018 Phase 1b multiple dose-escalating study completed, results announced in April 2020; Phase study 2 on hold
Indication(s)	Infectious and Parasitic diseases, including fungal and HIV
Dosage	Oral: 100 mg capsule format
Formulation	Lipid-based (not liposomal), includes Peceol, Gelucire and other GRAS approved excipients
IP position/Exclusivity	Oral delivery platform and formulation patents through 2038-2039, numerous countries Orphan status for VL.

iCo-019: Oral Amphotericin B Product Profile (2)

• **Positioning**	Safer, more practical oral formulation of a well-known broad spectrum antifungal Lower occurrence of resistance Lower impact on drug metabolism than other anti-fungals
• **Superior safety profile**	No infusion-related toxicity due to oral dosing No observed kidney nor liver toxicity to date
• **Equal efficacy**	Potential to retain potency Tissue distribution indicates drug accumulation over time; PK in Phase 1 and 1b demonstrated prolonged plasma half-life and increased AUC compared to closest oral competitor
• **Patient convenience/compliance**	No multiple IV infusions or IM injections. Reduction in cost and infrastructure to administer
• **Current activities**	Completed Phase 1b study using multiple dosing (Aus)
• **Next Step**	Phase 2 clinical study in VVC (more detail slide 52)

Opportunities to increase accessibility

Most effective treatment is parenteral amphotericin B resulting in:	Oral amphotericin B overcoming barriers to treatment:
1. Loss of income due to hospitalization for IV therapy	1. Easy to administer/at home administration
2. High cost of administration	2. Decreased cost of administration
3. Risk of infusion-related side effects	3. Lack of Infusion-related side effects (i.e. fever, chills etc.)
4. Risk of systemic toxicity	4. Lack of kidney, liver and GI toxicity
5. Limited accessibility	5. Increased accessibility
6. Not heat stable	6. Thermal stability at tropical temperatures

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