A MULTICENTRE COMPARATIVE TRIAL OF EFFICACY AND SAFETY OF SODIUM STIBOGLUCONATE (SSG), PAROMOMYCIN (PM) AND THE COMBINATION OF SSG AND PM AS FIRST-LINE TREATMENT FOR VISCERAL LEISHMANIASIS IN EAST AFRICA - LEAP 0104

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

ASTMH meeting

November 2010
Atlanta, USA
LEAP study group

Presenter: Dr Ahmed Mudawi Musa
Institute of Endemic Diseases,
University of Khartoum
Chairperson of LEAP

Objectives of LEAP 0104

- **Registration of PM as new treatment for VL in East Africa (Sudan, Ethiopia, Kenya & Uganda - as supported by data)**
- **Evaluation of shorter course (17 days) combination of PM+SSG as alternative treatment for VL**
- **Capacity building**

Study Design

- Open label phase III multicentre randomized controlled trial
- Treatments
  - Reference standard arm: SSG 20mg/kg given im/iv
  - Test arm 1: PM sulphate 20mg/kg im for 21 days (initially 15mg/kg)
  - Test arm 2: SSG (20mg/kg) & PM (15m/kg) combination for 17 days
- Assuming 85% efficacy in the reference arm (SSG), the trial was powered to test for a 15% difference between SSG and PM and 10% difference between SSG and Combination with 90% power and assuming 10% loss to follow-up, 10% HIV positivity:
  - Standard versus test arm 1= 195 patients per arm required
  - Standard versus test arm 2= 404 patients per arm required

Study Design

- Primary efficacy endpoint:
  - parasitology at 6m post EOT assessment
  - measured by visualization of parasites in tissue samples on microscopy
  - cure= absence of parasites at 6 months follow-up, provided no rescue medication was given during treatment or follow-up period
- Safety: AEs, SAEs, and deaths per arm
- An ITT and PP complete case analysis (missing data excluded) will be presented here (worst case analyses were also performed)

Inclusion/ Exclusion Criteria

Inclusion Criteria

- Clinical signs and symptoms of VL and the confirmed diagnosis by microscopy of tissue aspirates
- Age between 4 and 60 years (inclusive)
- Written informed consent

Exclusion Criteria

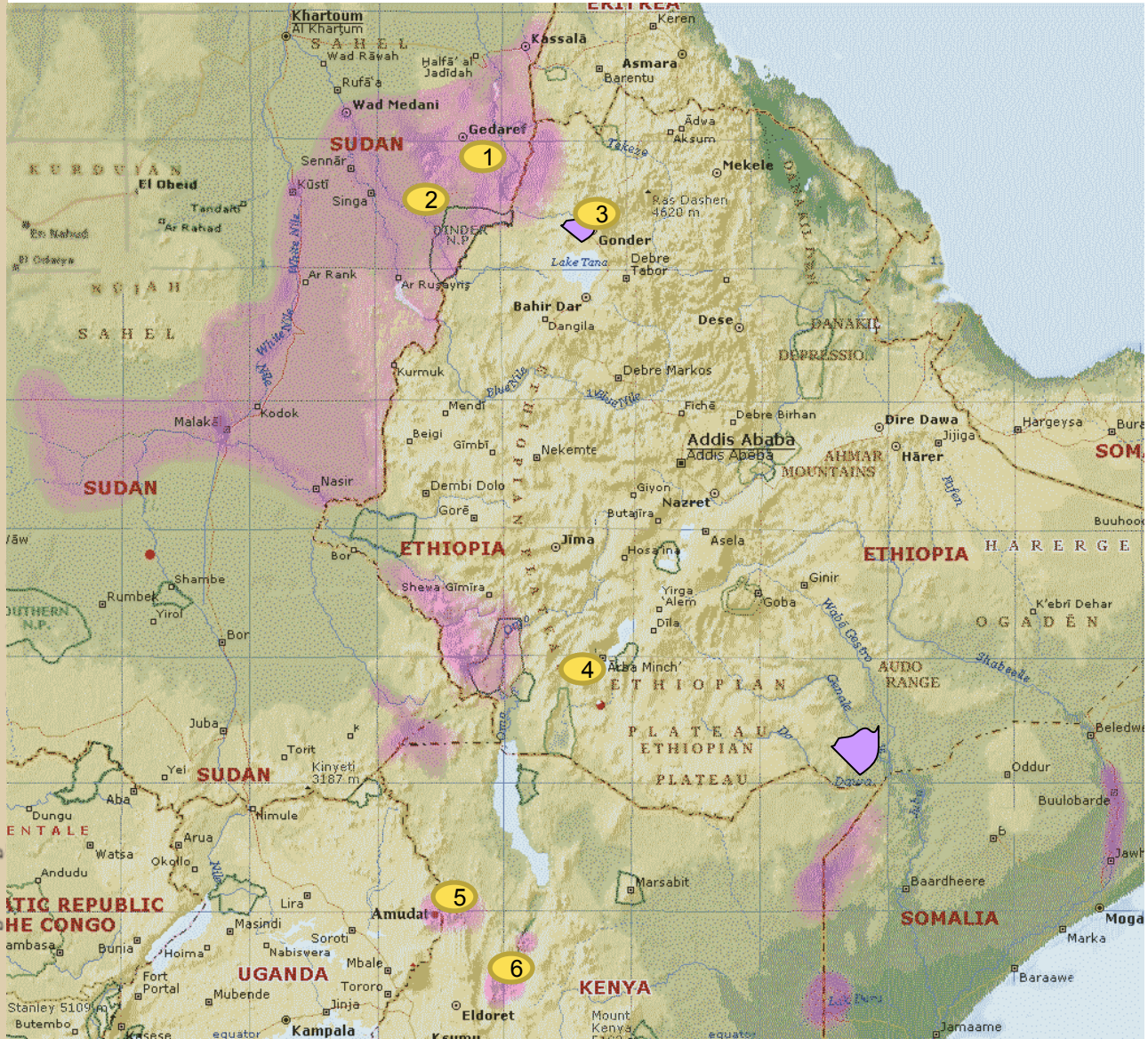
- Intake of any anti-leishmanial drug in the previous 6 months
- Pregnant or lactating women
- Pre-existing clinical hearing loss
- Serious underlying disease
- Severe protein and/or caloric malnutrition (Kwashiorkor or marasmus)
- Previous hypersensitivity reaction to SSG or aminoglycosides
- Concomitant severe infection (except HIV)
- Other conditions associated with splenomegaly
- History of cardiac arrhythmia or an abnormal ECG
- Haemoglobin <5 g/dL or WBC count <1 x $10^3/mm^3$
- Platelets < 40,000/mm^3
- Liver function tests more than 3 x ULN
- Serum creatinine outside the normal range

Schedule of assessment

Assessment	Day of Treatment					Follow-up	
	0 days	7 days	14 days	21 days (SSG only)	End of Treatment	3 months	6 months
Efficacy, Parasitology	✓				✓	✓	✓
ECG and Audiometry	✓		✓		✓	✓	✓
Biological Parameters	✓	✓	✓	✓	✓	✓	✓

- End of treatment assessment:
  - Day 31 for SSG
  - Day 22 for PM
  - Day 18 for combination
- Efficacy - Measured at 3 months if patient were clinically unwell
- ECG and audiometry were also carried out on D7 and D21 in Kenya and Kassab (audiometry was not done in Um El Kher)
- Biological Parameters: temperature, spleen & liver size, weight, Hb, plt, WBC, heart rate, blood pressure, bilirubin, BUN, creatinine, ALT, AST, amylase (Arba Minch only), AP(excluding Kassab)

LEAP Participating Centres in 0104



1 Kassab Hospital, University of Khartoum, *Sudan*

2 Um el Kehr centre, MSF-Holland, *Sudan*

3 Gonder Hospital, Gonder University, *Ethiopia*

4 Arba Minch Hospital, Addis Ababa University, *Ethiopia*

5 Amudat Hospital, Makerere University, *Uganda*

6 Centre for Clinical Research, KEMRI, *Kenya*

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

Best Science for the Most Neglected

DNDi
Drugs for Neglected Diseases initiative

Background

Best Science for the Most Neglected

2004 | 2005 | 2006

Nov | Q1 | Jul | Jun | Sep | Nov

Recruitment starts: LEAP 0104A

Lack of Efficacy

1st LEAP PI Meeting
Explore reasons for inefficacy

2nd LEAP PI Meeting
Review data from preliminary analysis of dose-ranging study

Recruitment LEAP 0104B restarts at increased PM dose

Next steps
Proposed dose-ranging study in Sudan
15mg/kg PM for 28 days
20mg/kg for 21 days

LEAP Group proposal for LEAP 0104B
Restart trial with increased dose of PM (20mg/kg) for 21 days

iOWH register PM in India 15mg/kg for 21 days

- PM 15mg/kg efficacy in 0104A=64% overall (14% and 47% in Sudan)
- Dose-ranging study efficacy was around 80% in the two arms

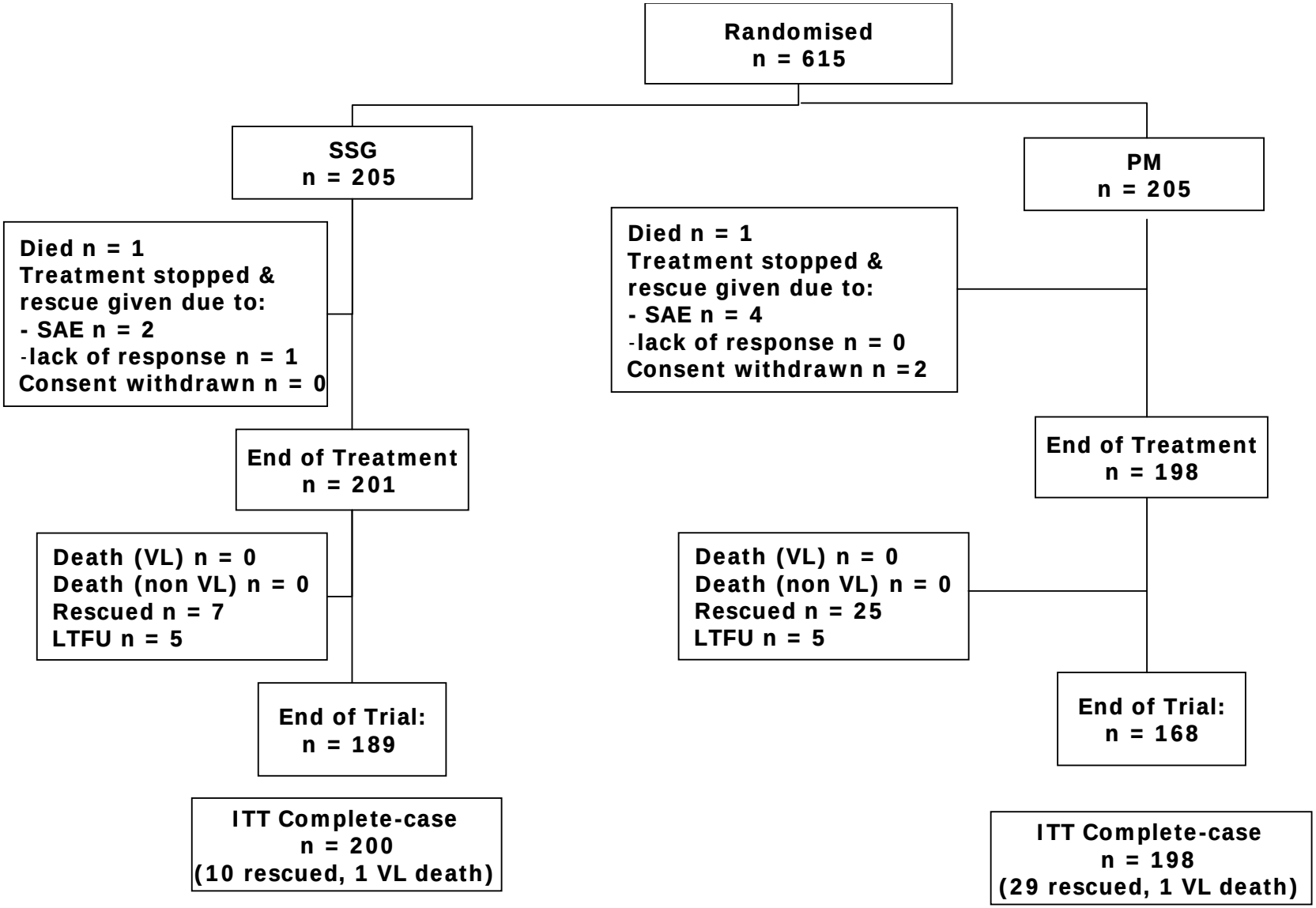
DNDi Drugs for Neglected Diseases initiative

Patients screened & reasons for exclusion

Total N° of patients screened	2862
Total number enrolled	1107
Total number failed screening	1755

Reason for Screen failure	Number of patients excluded
Negative aspirate for VL or contraindication for aspirates	953
Aberrant laboratory values	215
Age below 4 years or above 60 years	123
Pregnant/Lactating	48
Clinical hearing loss	18
Severe malnutrition	18
Refused to provide consent	17
Concomitant illness	17
Patients unable to attend follow-up	12
Others	334
Total	1755

Analysis 1: SSG v PM



Analysis 1: Baseline data

		SSG (N = 205)	PM (N = 205)
Age (years)	**Mean (SD)**	14.5 (8.9)	15.3 (9.9)
	4 - 17, n (%)	149 (72.7)	143 (69.8)
	≥18, n (%)	56 (27.3)	60 (30.2)
Sex, n (%)	**Female**	64 (31.2)	80 (39.4)
Weight (Kg)	**mean (SD)**	32.2 (14.3)	33.1 (15.5)
Temperature (°C)	**mean (SD)**	38.4 (1.0)	38.4 (1.0)
Heart Rate, (beats/min)	**mean (SD)**	113.2 (14.1)	111.7 (14.4)
Spleen Size (cm)	**mean (SD)**	7.5 (5.4)	7.7 (5.0)
Parasite Count, (log Scale), n (% of randomised)	**6+**	12 (5.9)	10 (4.8)
	5+	23 (11.2)	25 (12.2)
	4+	20 (10.0)	19 (9.3)
	3+	15 (7.3)	19 (9.3)
	2+	27 (13.2)	24 (11.7)
	1+	108 (52.7)	108 (52.7)
Haemoglobin (g/dL)	**mean (SD)**	7.9 (1.6)	7.9 (1.8)
AST (U/L)	**mean (SD)**	34.5 (24.3)	34.7 (25.2)
ALT (U/L)	**mean (SD)**	23.5 (16.4)	22.8 (16.6)
Creatinine (µmol/L)	**mean (SD)**	60.1 (28.3)	57.4 (28.8)

Analysis 1: adverse events (AEs)

	SSG (N = 205)	PM (N = 205)
Patients with at least one AE		
At any time	140 (68.3)	126 (61.5)
Treatment emergent	117 (57.1)	107 (52.2)
During Follow-up	64 (31.2)	54 (26.3)
Patients with serious AEs*		
Total	6 (2.9)	8 (3.9)
Treatment emergent	6 (2.9)	7 (3.4)
During Follow-up	0	1 (0.5)
Adverse drug reaction	5 (2.4)	6 (2.9)
Unrelated to study drug	1 (0.5)	2 (1.0)
Discontinuation due to a SAE	2 (1.0)	4 (2.0)
Deaths	**1 (0.5)**	**1 (0.5)**

Data are number (%). *No patient had more than 1 SAE

Analysis 1: SAEs and Audiometry

- SAE
  - 5 of the 14 documented SAEs were due to elevation of hepatic enzymes
  - Death in the SSG arm was due to cardiotoxicity
  - Death in the PM arm was due to VL
  - The most common AEs were due to abnormal investigations: transient elevation in transaminases

- Audiometric Findings
  - One patient in the SSG arm and 2 in the PM arm had disabling hearing impairment (DHI)
  - There were audiometric shifts in 12 (3.0%) patients at EOT, with audiometric shifts remaining in 4 (1.0%) at 6 months follow-up
  - There were twice as many audiometric shifts in the PM arm compared with the SSG arm at EOT (Fisher's exact test p = 0.380)

Note:

- Audiometric shift = change in hearing level since baseline of ≥25 dB at ≥1 threshold frequency or ≥20 dB at ≥2 adjacent threshold frequencies
- DHI = average of ≥31dB in those under 15 years and of ≥41dB in those 15 & above, across frequencies 500, 1000, 2000, 4000Hz

Analysis 1: AEs occurring in more than 10% of patients

AEs by System Organ Class	SSG		PM	
	ADR	NR	ADR	NR
All AEs	**150**	**50**	**164**	**28**
GI Disorder, n(%)	17 (11.3)	7 (14)	17 (10.4)	0
General Disorders & Administration Site Conditions, n(%)	10 (6.7)	2 (4.0)	28 (17.1)	2 (7.1)
Infections and Infestations, n(%)	12 (8.0)	35 (70)	8 (4.9)	19 (67.9)
Investigations, n(%)	68 (45.3)	1 (2.0)	65 (39.6)	2 (7.1)
Respiratory, thoracic mediastinal disorders, n(%)	26 (17.3)	1 (2.0)	33 (20.1)	3 (10.7)

- AEs
  - Administration site conditions were largely due to injections site pain (well documented with both drugs)
  - There was more gastrointestinal-related AEs in the SSG arm, but the number related was the same

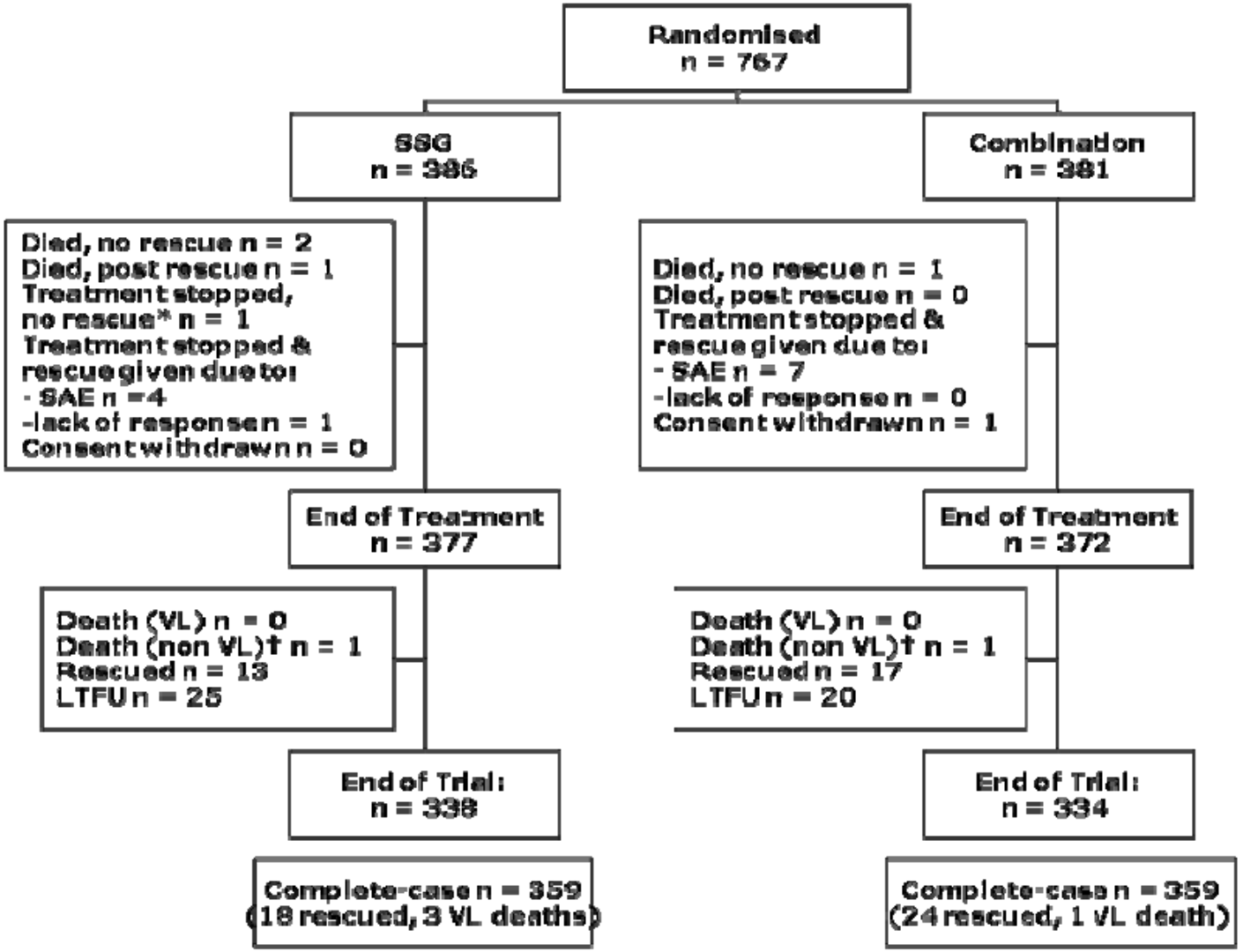
Analysis 1: Efficacy outcomes

	ITT		PP	
	SSG N = 200	**PM* N = 198**	**SSG N = 199**	**PM N = 197**
Efficacy at 6 months follow up, n (%)	188 (94.0)	167 (84.3)	188 (94.5)	166 (84.3)
Unadjusted difference between SSG and PM (95% CI), p- value*	9.7% (3.6 – 15.7%) p = 0.002		10.2% (4.2 – 16.2%) p = 0.001	
Test of difference between adults and children after adjustment for treatment: p- value**	0.569		0.426	

- Reasons for exclusions from PP analysis was due to incorrect treatment given

*p-value from Fisher's exact test
**p-value from likelihood ratio test comparing a model adjusting for treatment with a model that adjusts for treatment and age group

Analysis 2: SSG v Combination



LTFU = loss to follow-up
* Patient diagnosed with TB, subsequently LTFU
†Non VL deaths confirmed by medical co-ordinator

Analysis 2: Baseline data

		SSG (N = 386)	Combination (N = 381)
Age (years)	**Mean (SD)**	15.3 (9.3)	16.1 (9.4)
	4 - 17, n (%)	259 (67.1)	246 (64.6)
	≥18, n (%)	127 (32.9)	135 (35.4)
Sex, n (%)	**Female**	105 (27.2)	108 (28.4)
Weight (Kg)	**mean (SD)**	33.5 (14.5)	34.2 (14.7)
Temperature (°C)	**mean (SD)**	38.1 (1.1)	38.2 (1.1)
Heart Rate, (beats/min)	**mean (SD)**	108.2 (16.1)	107.3 (15.9)
Spleen Size (cm)	**mean (SD)**	8.1 (5.0)	8.0 (4.8)
Parasite Count, (log Scale), n (% of randomised)	**6+**	25 (6.5)	36 (9.5)
	5+	48 (12.4)	76 (20.0)
	4+	58 (15.0)	40 (10.5)
	3+	49 (12.7)	50 (13.1)
	2+	67 (17.4)	48 (12.6)
	1+	139 (36.0)	131 (34.3)
Haemoglobin (g/dL)	**mean (SD)**	7.9 (1.6)	7.9 (1.9)
AST (U/L)	**mean (SD)**	40.9 (26.7)	40.3 (29.3)
ALT (U/L)	**mean (SD)**	26.1 (17.4)	25.9 (20.0)
Creatinine (µmol/L)	**mean (SD)**	66.8 (28.1)	67.9 (28.6)

Analysis 2: adverse events (AEs)

	SSG (N = 386)	Combination (N = 381)
Patients with at least one AE		
At any time	271 (70.2)	251 (65.9)
Treatment emergent	237 (61.4)	207 (54.3)
During Follow-up	114 (29.5)	115 (30.2)
Patients with serious AEs*		
Total	17 (4.4)	16 (4.2)
Treatment emergent	14 (3.6)	16 (4.2)
During Follow-up	3 (0.8)	0
Adverse drug reaction	10 (2.6)	13 (3.4)
Unrelated to study drug	7 (1.8)	3 (0.8)
Discontinuation due to a SAE	4 (1.0)	7 (1.8)
Deaths	4 (1.0)	3 (0.8)

Data are number (%). *No patient had more than 1 SAE

Analysis 2: AEs occurring in more than 10% of patients

AEs by System Organ Class	SSG		Combination	
	ADR	NR	ADR	NR
All AEs	**291**	**156**	**263**	**85**
GI Disorder, n(%)	25 (8.6)	17 (10.9)	32 (12.2)	10 (11.8)
General Disorders and Administration Site Condition, n(5)	30 (10.3)	7 (44.9)	69 (26.2)	1 (1.2)
Infections and Infestations, n(%)	32 (11.0)	106 (67.9)	17 (6.5)	52 (61.1)
Investigations, n(%)	128 (44.0)	1 (0.6)	118 (44.9)	2 (2.4)

- AEs
  - The most common AEs were abnormal investigations: transient elevation in ALT & AST
  - Administration site conditions were largely (85%) due to injections site pain
  - PKDL occurred in 48 (12%) patients in the SSG arm and 23 (6%) patients in the combination arm

- Audiometric findings
  - There were audiometric shifts recorded in 5% of patients in each arm by end of treatment
  - In less than 1% of patients in the SSG arm and less than 4% of those in the combination arm, a shift remained at 6 months follow-up
  - One patient in each arm developed disabling hearing impairment

Analysis 2: SAEs narrative

- SAEs
  - The most common cause of SAEs
    - abnormal investigations - particularly liver enzymes (13/33)
    - concomitant infections (6/33)
    - renal impairment (4/33)
    - gastrointestinal disorders (3/33)
  - There were three deaths in the combination arm, one of which (cardiotoxicity) was considered drug-related
  - By comparison, three of the four deaths in the SSG arm were considered drug-related (one cardiotoxicity and two renal failures)

Analysis 2: Efficacy outcomes

	ITT		PP	
	SSG (N = 359)	Combination (N = 359)	SSG (N = 357)	Combination (N = 347)
Efficacy at 6 months follow-up, n (%)	337 (93.9)	328 (91.4)	336 (94.1)	317 (91.4)
Unadjusted difference between SSG and Combination (95% CI)	2.51% (-1.31 to 6.33%)		2.76% (-1.07 to 6.60%)	
Test of difference between treatment efficacy: p value*	0.198		0.157	
Test of difference across centres, after adjustment for treatment: p value*	0.337		0.286	
Test of difference between adults and children after adjustment for treatment: p Value*	0.122		0.080	

- Reasons for exclusions from PP analysis include: Low HB, Low WCC, incorrect treatment given, expired medication given

*p-value from likelihood ratio test, comparing models with and without variable being tested

Conclusions

- The difference in efficacy between PM and SSG is between 3.6% and 15.7%
- The combination appeared to be as efficacious and safe as the standard treatment with SSG with no differences seen between sites and countries
- The combination is cheaper and of shorter duration, thereby offering a potential advantage for health care providers and patients
- PKDL post treatment should be further evaluated for the combination
- Registration and recommendation of the combination is now ongoing in Sudan, Ethiopia, Kenya and Uganda

ACKNOWLEDGEMENTS

- **All our patients**
- **LEAP**: Universities of Khartoum, Addis Ababa, Gonder, Makerere, KEMRI; Ministries of Health of Kenya, Uganda, Ethiopia and Sudan; Drug regulatory authorities, LSH&TM; MSF; I+ Solutions
- **Donors**: Médecins Sans Frontières/Doctors without Borders, International; Ministry of Foreign and European Affairs (MAEE), France; Department for International Development (DFID), UK; Spanish Agency for International Development Cooperation (AECID), Spain; République and Canton de Genève, Switzerland; Region of Tuscany, Italy; Fondation Pro Victimis, Switzerland; Fondation André & Cyprien, Switzerland; a private foundation, and individual donors.

Best Science for the Most Neglected

DNDi Drugs for Neglected Diseases initiative