Background

- Leuprolide acetate (LA) is the standard of care LHRH agonist used to suppress testosterone to the level similar to bilateral orchiectomy for the treatment of prostate cancer[1]
- Multiple long-acting formulations are now available that utilize different technologies regarding their mode of delivery and absorption
- Two formulations available are a controlled-release subcutaneous (SC) LA formulated with ATRIGEL® Delivery System (ELIGARD®; SC-LA) and an intramuscular (IM) LA formulated with microspheres (LUPRON®; IM-LA); both formulations use 7.5 mg LA for their 1-month dose
- There has been no head-to-head study comparing the two different formulations of LA to determine whether there are pharmacokinetic (PK) or pharmacodynamic (PD) differences

1. Rick FG, et. al, Urol Oncol. 2015;33(6):270-274

Objectives

- To compare head-to-head the PK and PD profiles of SC-LA and IM-LA

Methods

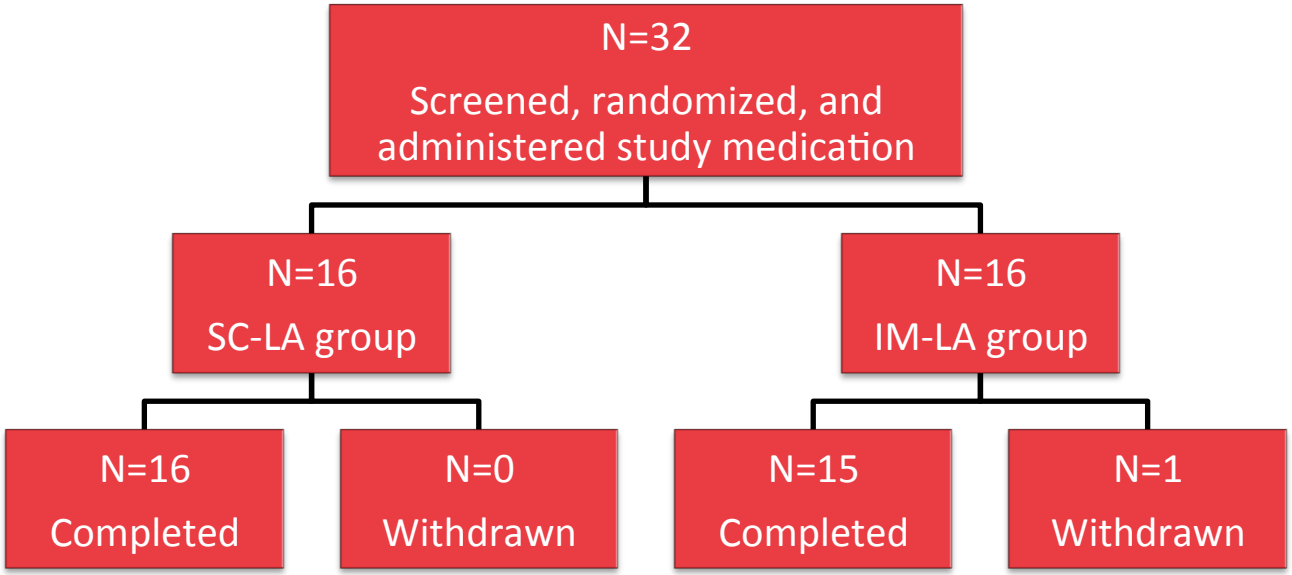
- 32 healthy male patients aged 18-55 years, n=16 in each treatment group
- Open-label, randomized, single-dose, analytically blinded, parallel-group
- Subjects were randomized to receive a single dose of either: 7.5 mg SC-LA or 7.5 mg IM-LA
- Serum LA, LH, and T were measured using HPLC-mass spectrometry, two-site immunochemiluminometric assay and radioimmunoassay, respectively
- PK parameters were determined from individual LA concentration-time data by non-compartmental analysis: Cmax, tmax, t1/2, AUC

1. Rick FG, et. al, Urol Oncol. 2015;33(6):270-274

Baseline Characteristics

Characteristic	SC-LA (n=16)	IM-LA (n=16)
Age, years	40.2 ± 8.3	36.4 ± 8.6
Weight, kg	79.3 ± 10.1	74.4 ± 9.6
Height, cm	182.1 ± 7.1	178.0 ± 3.8

Subject Disposition



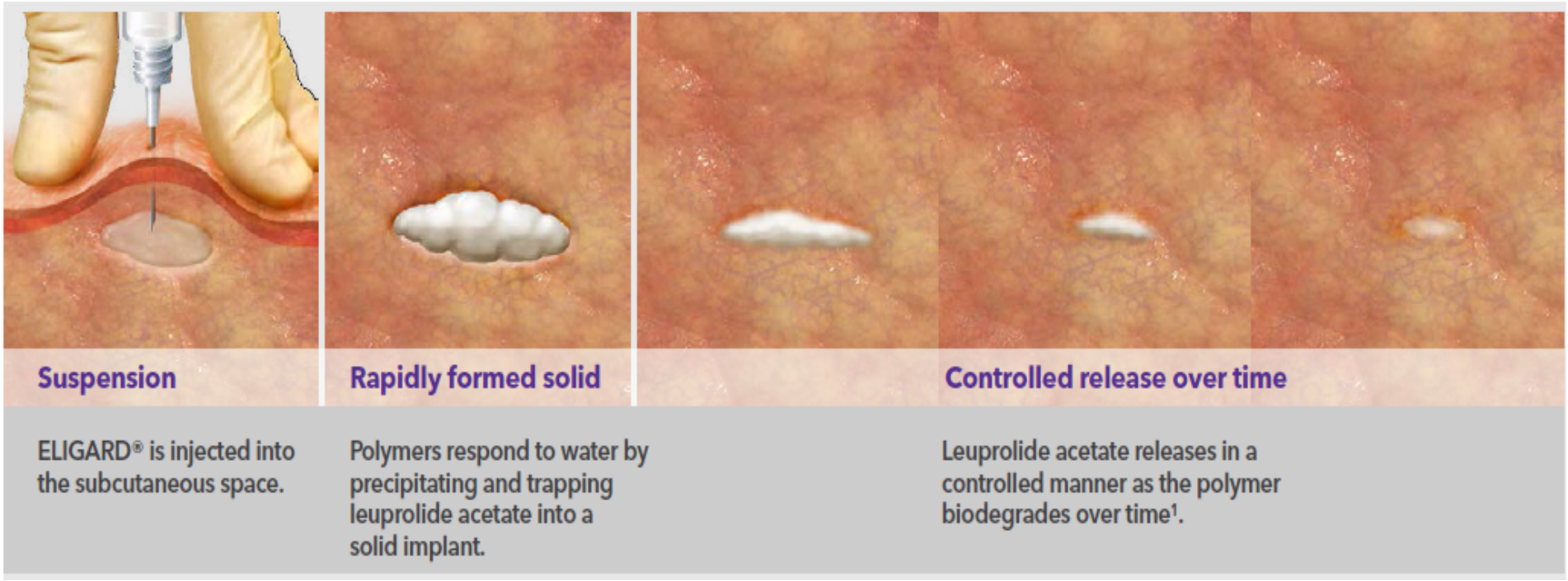
SOURCE: Manuscript Pending

Comparison of ATRIGEL® and Microsphere Technology

	Attributes	ATRIGEL®[1, 2, 3, 4]	Microspheres[5]
Efficacy	Compatibility with Wide Range of Pharmaceutical Compounds	✓	
Administration	Wide Variety of Injection Sites	✓	✓
	Minimally Invasive Delivery Technique	✓	
	Recoverable Dosage	✓	
Safety	Favorable Safety Profile	✓	✓
	Favorable Toxicity Profile	✓	✓
	Biocompatible	✓	✓
	Biodegradable	✓	✓

SOURCE: 1. http://www.qltinc.com/development/technologies/atrigel.html; 2. Tombal et al. European Urology Supplements 2005: 30-36; 3. Sasse et al. Rev Bras Med 2014: 135-141; 4. Berges, Eur Urol Suppl 4 (2005) 20–25 ; 5. Kim et al. Springer Biotech: 2006

ATRIGEL® Technology: Liquid Solutions form One Solid Depot in Situ

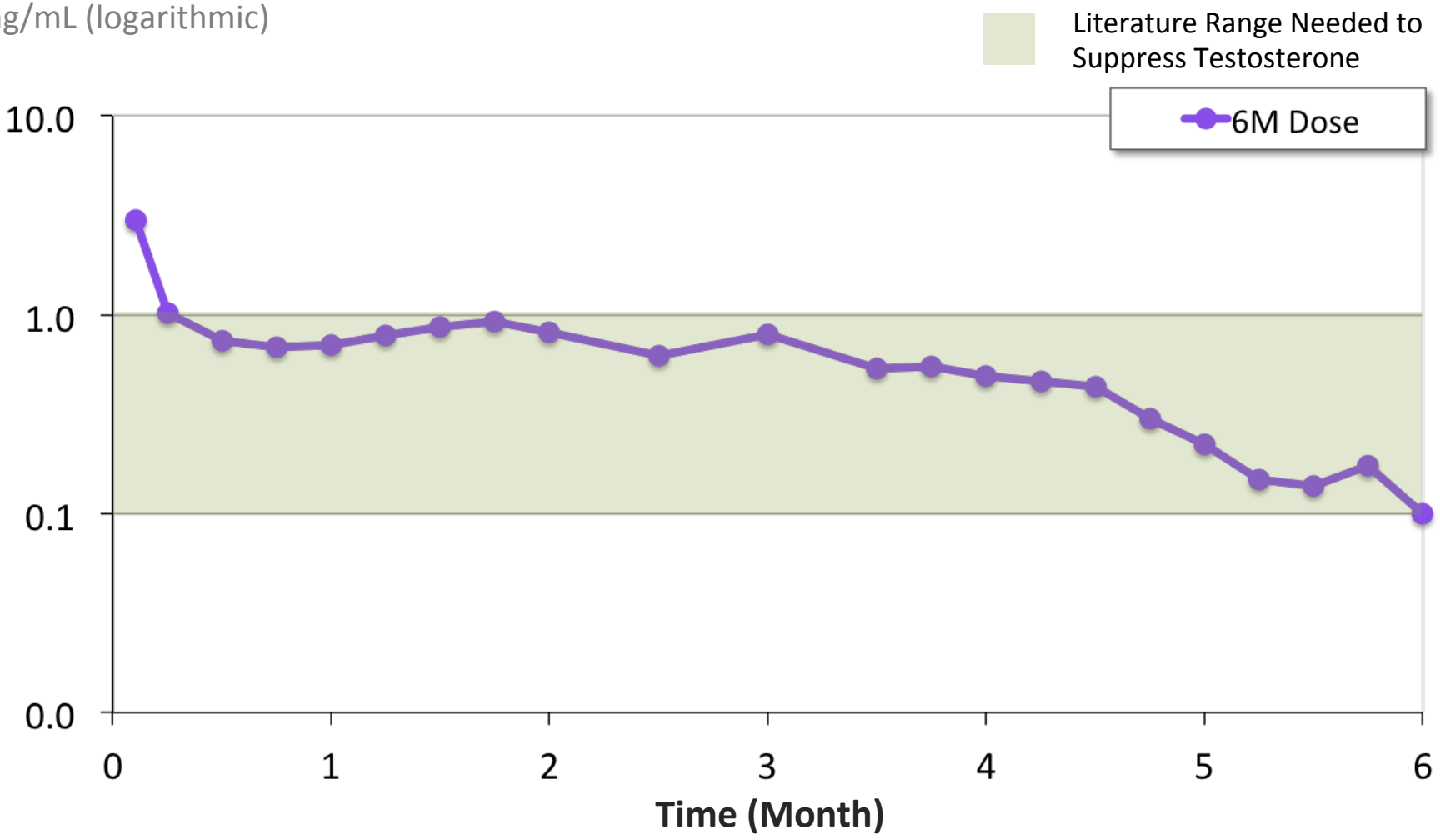


SOURCE: http://www.tolmar.com.au/img/eligard/delivery.jpg

ATRIGEL® Technology Allows for Controlled Release of Drug

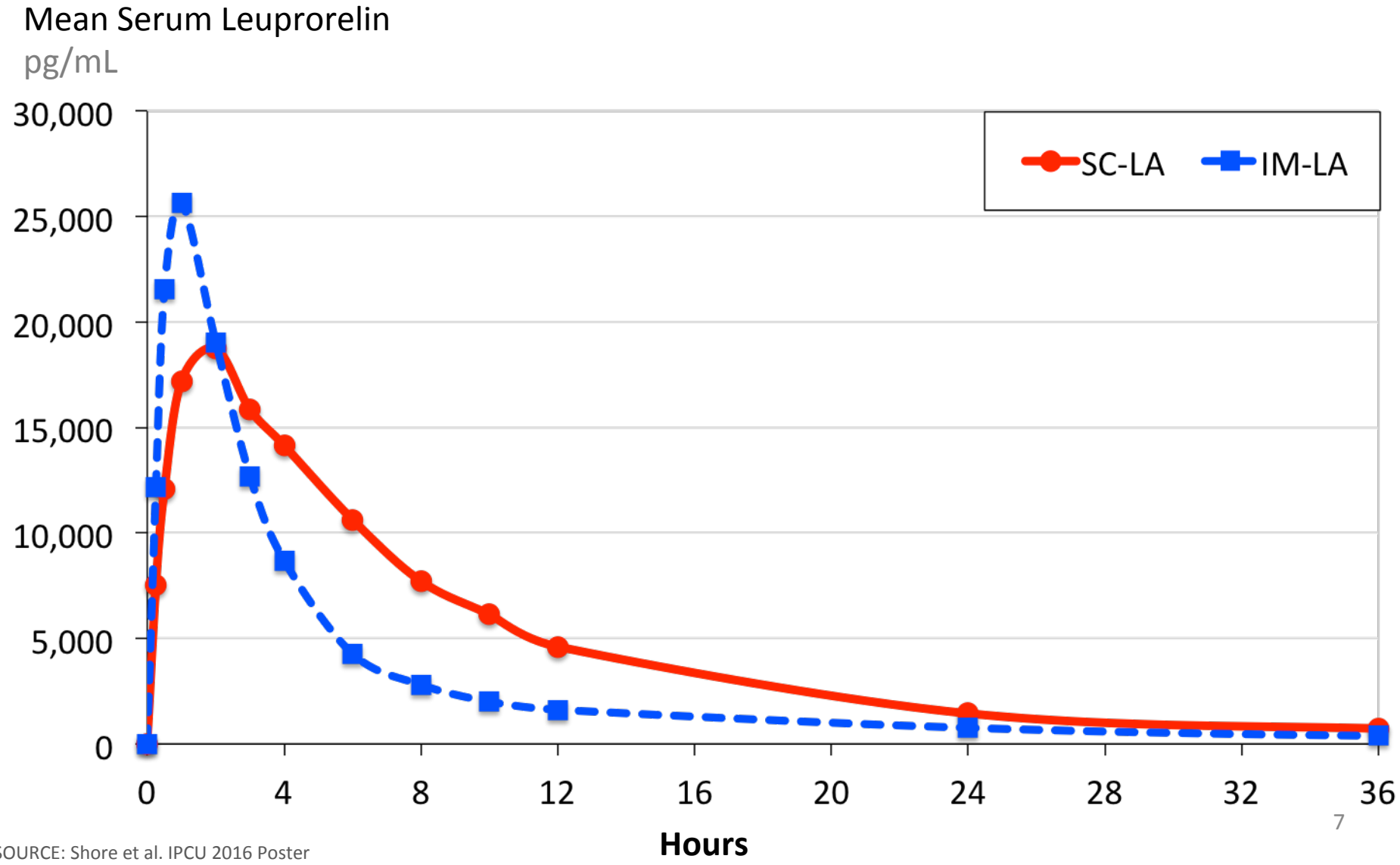
Median Serum Leuprolide Concentration Over Time During Plateau Phase (Days 3-168)

ng/mL (logarithmic)



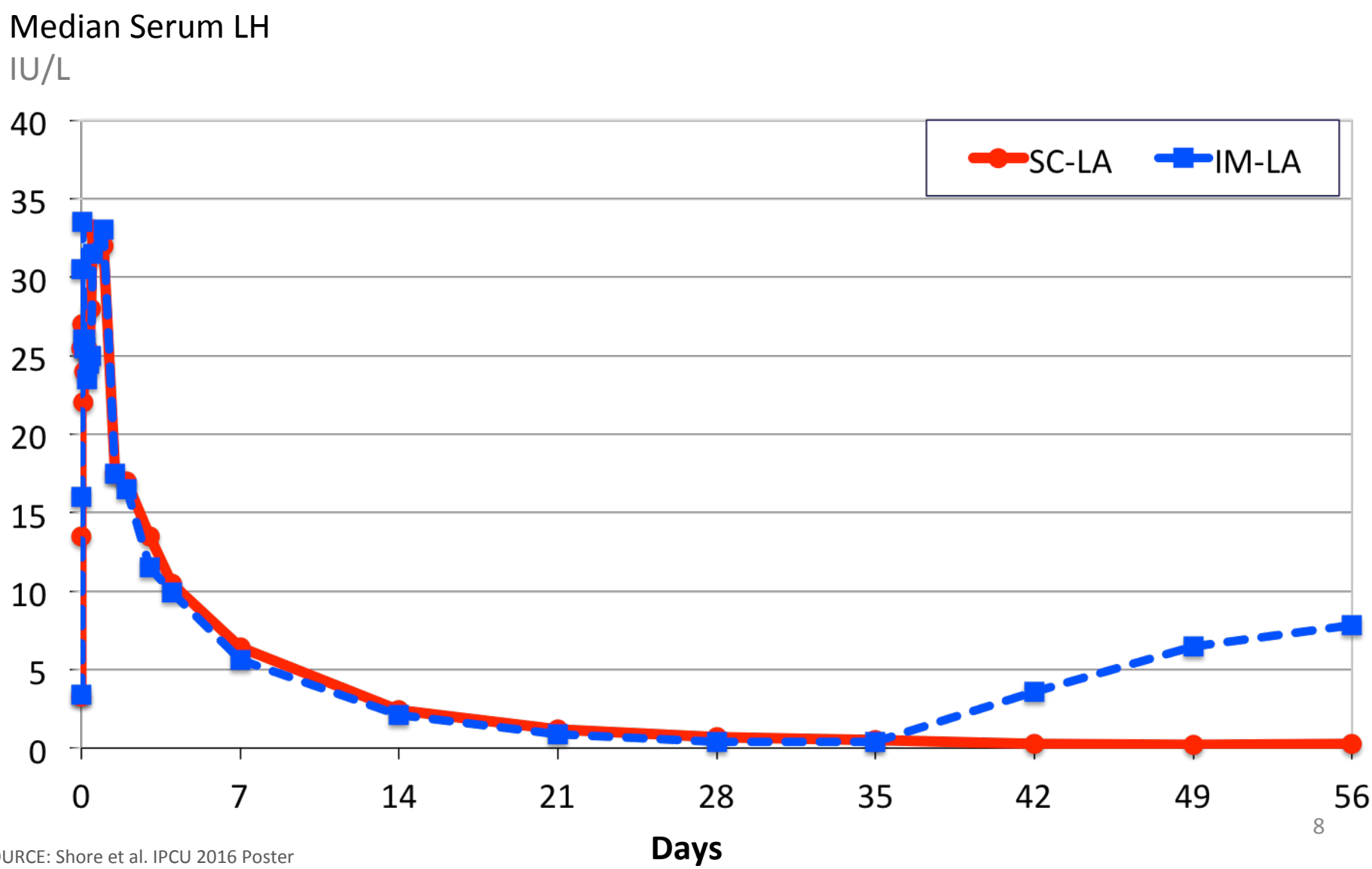
SOURCE: ELIGARD® 6 Month CSR (Data on File).

Mean serum LA curves for SC-LA exhibited a lower initial surge and smaller slope of decline compared to IM-LA



SOURCE: Shore et al. IPCU 2016 Poster

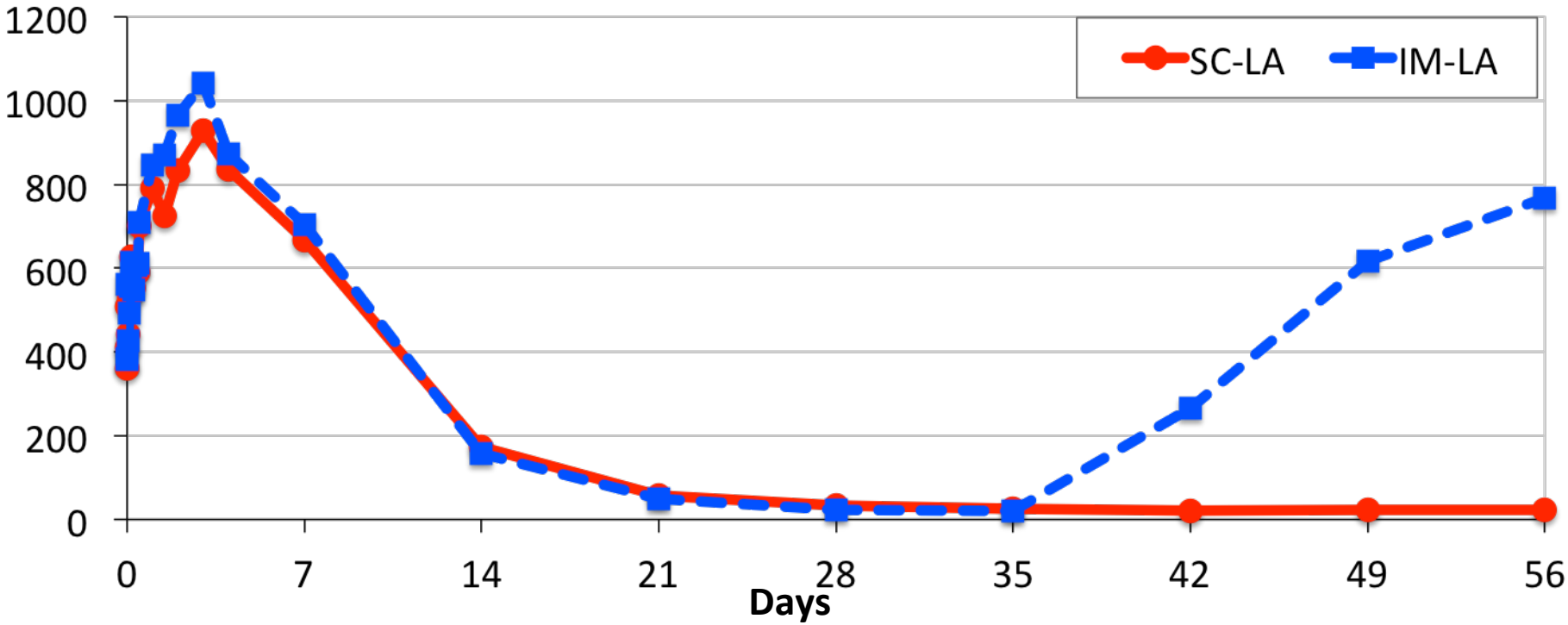
Median serum LH for subjects treated with IM-LA began to rise after day 35 whereas SC-LA serum LH levels remained low through day 56



SOURCE: Shore et al. IPCU 2016 Poster

Serum Testosterone was well suppressed in SC-LA after Day 35

Median Serum Testosterone
ng/dL



- Serum T levels began to **recover** after day 35 in IM-LA treated subjects
- Serum T levels were **consistently suppressed** through day 56 in SC-LA treated subjects

SOURCE: Shore et al. IPCU 2016 Poster

Both products exhibited safety profiles as expected for all LHRH agonists

System Organ Class	Number of Events	
	SC-LA 7.5 mg (n=16)	IM-LA 7.5 mg (n=16)
Body as a whole, including injection-site	43	7
Cardiovascular systems	13	12
Digestive system	6	3
Metabolic and nutritional disorders	2	1
Nervous system	14	13
Respiratory system	2	3
Skin and appendages	5	6
Urogenital tract	10	1

No trends for clinically relevant abnormalities of laboratory results observed

SOURCE: Shore et al. IPCU 2016 Poster

Conclusion/Discussion (1 of 2)

- All LHRH formulations have the objective of delivering stable dosing over a prescribed time interval, and utilize different technologies regarding their mode of delivery and absorption
- Misperceptions persist that all LH-RH formulations are the same and interchangeable, but they are likely not
- In this study, two formulations of LA, SC and IM, were tested and different PK and PD profiles are observed
- The PK of SC-LA exhibited a lower initial surge of LA concentration and extended release kinetics compared to IM-LA
- A single SC-LA dose had a longer duration of detectable LA compared with a single dose of IM-LA, indicating a more consistent delivery of drug over time

Conclusion/Discussion (2 of 2)

- SC-LA suppressed LH and T for a longer duration compared to IM-LA, despite the same amount of active drug
- Both products exhibited safety profiles as expected for all LHRH agonists, with no trends for clinically relevant abnormalities of laboratory results
- Subjects treated with SC-LA experienced up to 56 days of serum LH and T suppression
- Data suggests that the 1-month formulation of SC-LA may prevent T escapes in between SC-LA doses if the patient is delayed in receiving their next dose
- SC-LA could provide increased patient flexibility as U.S. payers don't allow patients to receive a subsequent LHRH injection before the prescribed dosing interval has been completed, and it may be difficult to schedule a visit for the exact day when the next injection is allowed