

# 6-Month GnRHa Formulations Are a Good Choice During the COVID-19 Pandemic and Beyond

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## INTRODUCTION

- Achieving/maintaining effective hormone suppression is fundamental in treating central precocious puberty (CPP)
- CPP patients are vulnerable to late dosing as they cannot self-administer and require clinic/hospital visits for injections, currently exacerbated by COVID-19
- In children, the hypothalamic-pituitary-gonadal axis may rebound<sup>1</sup> faster than elderly oncology patients, so hormone escapes are possible with late dosing
- The stimulatory flare from gonadotropin-releasing hormone agonists (GnRHa)<sup>2</sup> increases risk of escapes with late injections
- Longer duration formulations demonstrating hormone suppression through the dosing interval should be considered
- 6-month formulations typically require two office visits per year with only two opportunities to be 'late'
- A novel 6-month small-volume, subcutaneously administered GnRHa treatment for CPP approved in 2020<sup>3</sup> effectively suppressed pubertal hormones and pubertal progression<sup>4</sup>

## OBJECTIVE

- The first study evaluated efficacy and safety of 6-month 45-mg subcutaneous leuprolide acetate for CPP
- As large numbers of CPP patients are not present in real-world databases, we present data from a second study in prostate cancer (PCa) patients treated with drugs with the same active ingredient and similar mechanism of action to determine the scope and impact of late injections of androgen deprivation therapy
- The second study in PCa patients evaluated:
  - Timeliness of LHRH agonist dosing
  - Subsequent rate of T breakthroughs above 20 ng/dL

## METHODS

- CPP Study
  - Sixty-two children (60 girls, 2 boys) with treatment-naïve CPP received 2 doses of 45 mg subcutaneous leuprolide acetate at 24-week intervals
  - Calculate the percentage of children with serum luteinizing hormone (LH) <4 IU/L 30 minutes following GnRHa stimulation at week 24
- PCa Study
  - A retrospective analysis (1/1/07-6/30/16) of US oncology/urology hospitals, multispecialty practices, small group practices and physician offices EMR of PCa patients receiving GnRHa injections (n=85,030) was conducted to evaluate the frequency of late injections and testosterone (T) >20 ng/dL (target levels in PCa)
  - Mean late doses/year for 1, 3, 4, 6-month GnRHa doses were calculated by multiplying late dose proportion and number of doses/year
  - Late dosing was defined as occurring after days 33, 98, 129, 195, respectively

## RESULTS

- CPP Study
  - Mean age at onset of treatment was 7.5±0.1 years (Table 1)
  - LH levels of <4 IU/L were achieved by ≥85% of children at each timepoint (Figure 1)
  - All but 2 children achieved suppression of E2 <20 pg/mL (58/60; 97%) or T <28.4 ng/dL (2/2; 100%) at week 24, meeting predefined prepubertal targets (Table 2)
- PCa Study
  - Patient demographics were well-balanced across all subgroups (Table 3)
  - 27% of GnRH agonists were administered later than scheduled
  - Number of late doses/year for 1, 3, 4, 6-month GnRHa formulations were 5.4, 0.8, 0.8, 0.6, respectively (Table 4)
  - 43% of testosterone values exceeded 20 ng/dL for late injections compared to only 21% for early/on-time injections (Figure 2)

Table 1. CPP Study Baseline Demographics

	Population		
	Safety <sup>1</sup> (N=64)	ITT <sup>2</sup> (N=62)	Protocol <sup>3</sup> (N=43)
Age Mean	7.5	7.5	7.3
Sex Female % (n)	96.9(62)	96.8(60)	97.7 (42)
White % (n)	53.1(34)	51.6(32)	41.9 (18)
Black or African American % (n)	23.4(15)	24.2(15)	25.6 (11)
American Indian or Alaska Native % (n)	7.8(5)	8.1(5)	11.6 (5)
Race Asian % (n)	4.7(3)	4.8(3)	4.7 (2)
Native Hawaiian or Other Pacific Islander % (n)	1.6(1)	1.6(1)	2.3 (1)
Unwilling to Provide % (n)	1.6(1)	1.6(1)	2.3 (1)
Other % (n)	7.8(5)	8.1(5)	11.6 (5)

Figure 1. CPP Study Mean (±SE) Peak LH Level and Proportion of Children Who Achieved Peak LH <4 IU/L (ITT Population)

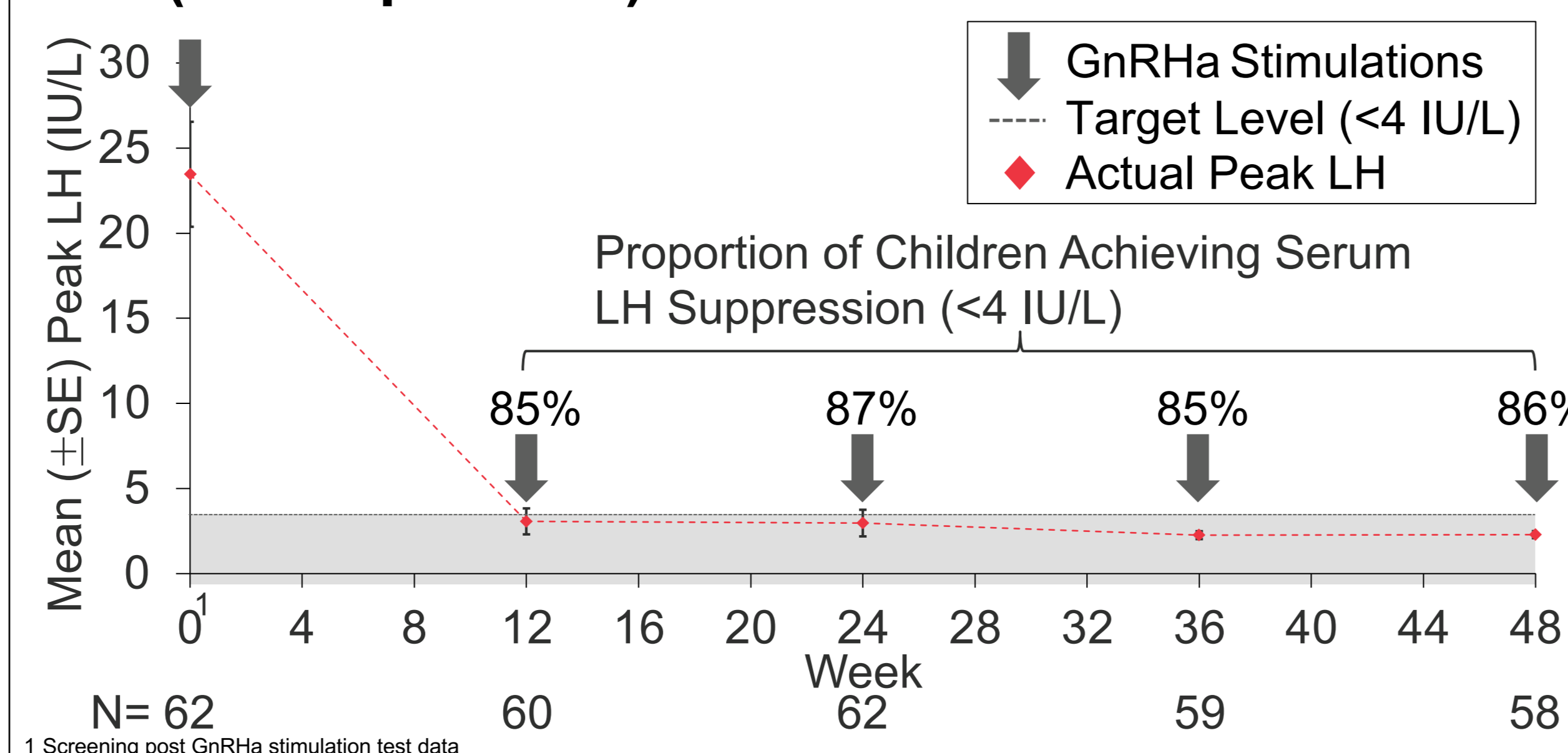


Table 2. CPP Study Proportion of Children Achieving Serum Hormone Suppression (ITT Population) (N=62)

Endpoints <sup>1</sup>	% (n/N) of Patients Achieving Endpoints <sup>1</sup>			
	Week 12	Week 24	Week 36	Week 48
LH <4 IU/L	85 (51/60)	87 (54/62) <sup>2</sup>	85 (50/59)	86 (50/58)
Estradiol levels <73.4 pmol/L (<20 pg/mL)	98 (56/57)	97 (58/60)	98 (56/57)	98 (55/56)
Testosterone levels <1 nmol/L (<28.4 ng/dL)	100 (2/2)	100 (2/2)	100 (2/2)	100 (1/2)
FSH levels <2.5 IU/L	62 (37/60)	66 (41/62)	44 (26/59)	55 (32/58)

<sup>1</sup> Post GnRH agonist stimulation  
<sup>2</sup> Primary Efficacy Endpoint

Table 3. PCa Study Patient Demographics – Age and Race (n=22,845<sup>1</sup>)

		Formulation			
		1-Month 7.5 mg (n=3,175)	3-Month 22.5 mg (n=7,065)	4-Month 30 mg (n=7,359)	6-Month 45 mg (n=5,246)
Age Mean		73.3	73.0	74.5	74.6
Race	White % (n)	76.8 (2,439)	73.6 (5,200)	73.2 (5,390)	77.8 (4,080)
	Black % (n)	11.2 (356)	10.5 (741)	14.6 (1,075)	11.8 (617)
	Asian % (n)	1.4 (44)	3.3 (231)	1.1 (84)	1.1 (57)
	Other % (n)	10.6 (336)	12.6 (893)	11.0 (810)	9.4 (492)

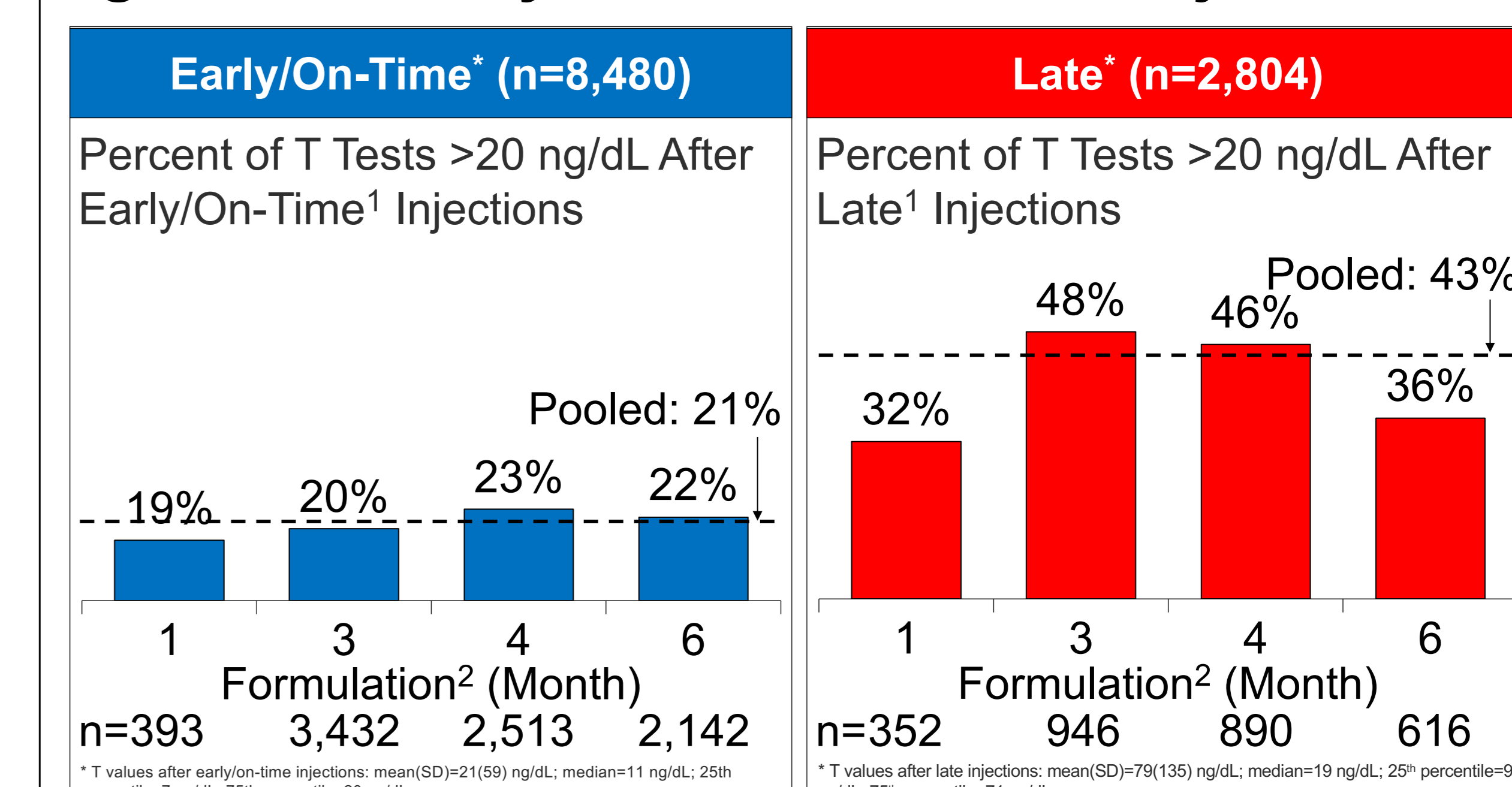
<sup>1</sup> Excluded 15 patients missing age data

Table 4. PCa Study Illustration of Expected Number of Late Injections per Year by Formulation

	Formulation			
	1-Month	3-Month	4-Month	6-Month
Number of Injections per Year (n)	12	4	3	2
Likelihood of Being Late per Injections (%)	45	21	27	28
Expected Number of Late Injections per Year (n)	12*45% =5.41	4*21% =0.82	3*27% =0.80	2*28% =0.57

<sup>1</sup> "Early/on-Time" if on/prior to, or "Late" if after day 32 (1M), 97 (3M), 128 (4M), or 194 (6M)

Figure 2. PCa Study Proportion of T Tests >20 ng/dL After Early/On-Time<sup>1</sup> and Late<sup>1</sup> Injections



<sup>1</sup> "Early/On-Time" if prior to, or "Late" if on/after day 33 (1-M formulation), 98 (3-M formulation), 129 (4-M formulation), or 195 (6-M formulation)  
<sup>2</sup> First admin data for 1-M formulation was excluded to remove skewed results from potential T flare seen with LHRH agonists

## CONCLUSIONS

- A small volume of 45-mg subcutaneous leuprolide acetate administered at a 6-month interval effectively suppressed pubertal hormones
- This long-acting GnRHa preparation of leuprolide acetate is a new and effective therapy for children with CPP
- 6-month GnRHa formulations require fewer visits for treatment, which will likely be preferred by patients and clinicians, especially during a pandemic
- 6-month formulations had fewer late doses/year vs. 1, 3, 4-month formulations
- Late injections were correlated with ineffective T suppression: T levels were >20 ng/dL over 40% of the time
- Late dosing increased the proportion of T >20 ng/dL compared to early/on-time dosing

## IMPLICATIONS

- The 45-mg, subcutaneous formulation of leuprolide acetate is the first leuprolide acetate therapy with a polymeric gel delivery system and a small injection volume administered subcutaneously every 6 months, and represents an effective and convenient addition to existing treatment options for children with CPP
- Clinicians should ensure dosing is on time or consider using 6-month formulations that have less frequent opportunities for late dosing and demonstrate/maintain efficacy through the labelled dosing period
- This will give greater confidence of continued hormone suppression when dosed late
- Similar studies should be conducted to assess the impact of late dosing of GnRHa in CPP patients

## References:

- Kuiri-Hänninen T. et al., *Horm Res Paediatr.* 2014
- Shore ND. et al., *Prostate Cancer Prostatic Dis.* 2013
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