Mike Smith
Manager of Clinical Projects ZARS inc.

Clinical development of Rapydan

ZARS PHARMA

Specialty Pharmaceutical Technologies

We are a specialty pharmaceutical company focused on the development and commercialization of patented technologies that deliver drugs into and across the skin. Our primary therapeutic targets are pain management and dermatology.

RAPYDAN

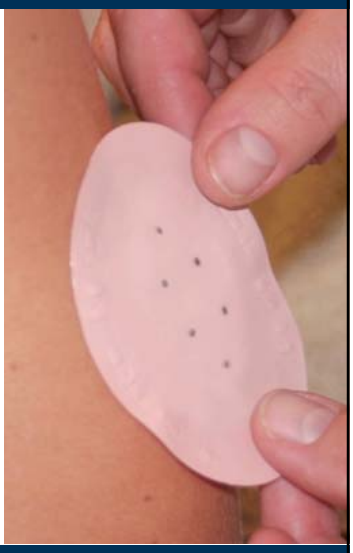
RAPYDAN

INDICATION

Children 3 and over: For surface anesthesia of the skin in connection with needle puncture on normal intact skin.

DESCRIPTION

- Integrated patch with CHADD and eutectic mixture of lidocaine and tetracaine
- *3*0-minute application
- Long duration of action
- Vasodialation



RAPYDAN

INTELLECTUAL PROPERTY
- CHADD family of patents
- Local anesthetic formulation

STATUS
- US NDA approved in 2005
- Favorable PI/SPC
- Sweden MPA approved March 2007
- MRP Ongoing

PARTNER EUSAPharma

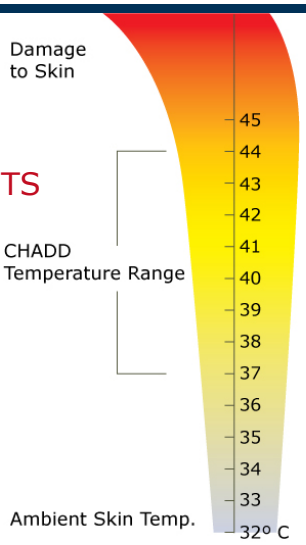
CHADD™

INNOVATION: Controlled Heat-Assisted Drug Delivery

Heat increases:
- Skin permeability
- Body fluid circulation
- Blood vessel wall permeability
- Drug solubility in formulation
- Drug release rate

CHADD

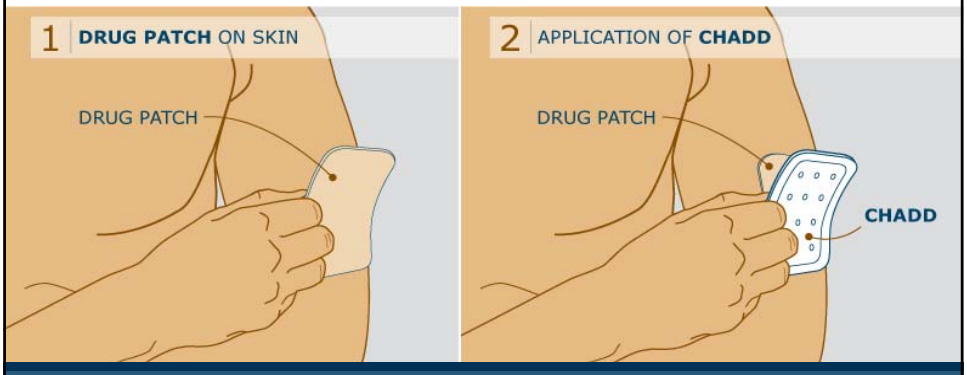
SKIN TEMPERATURE TARGETS



CHADD

HOW DOES IT WORK?

- Controlled Temperature
  oxygen
- Controlled Duration of Heating
  amount of chemicals



CHADD

THERAPEUTIC ADVANTAGES

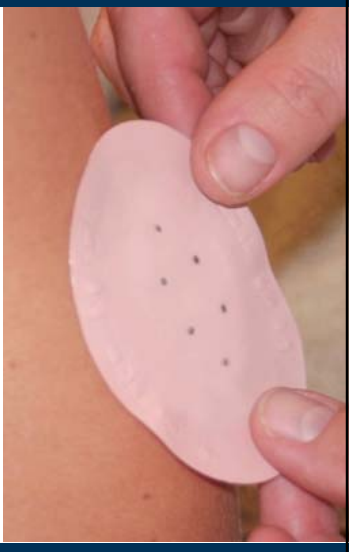
- On demand, incremental dosing
- Shorter onset time to therapeutic concentration

RAPYDAN

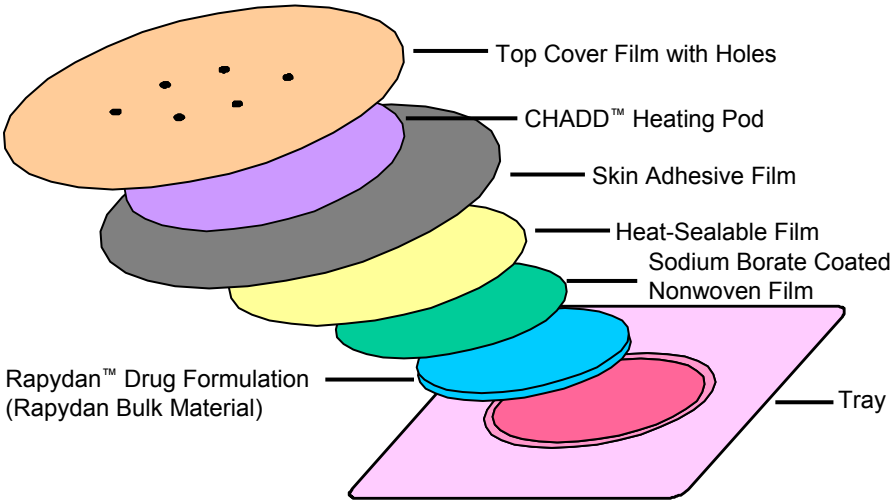
TERMINOLOGY

- S-Caine
- Synera
- Rapydan

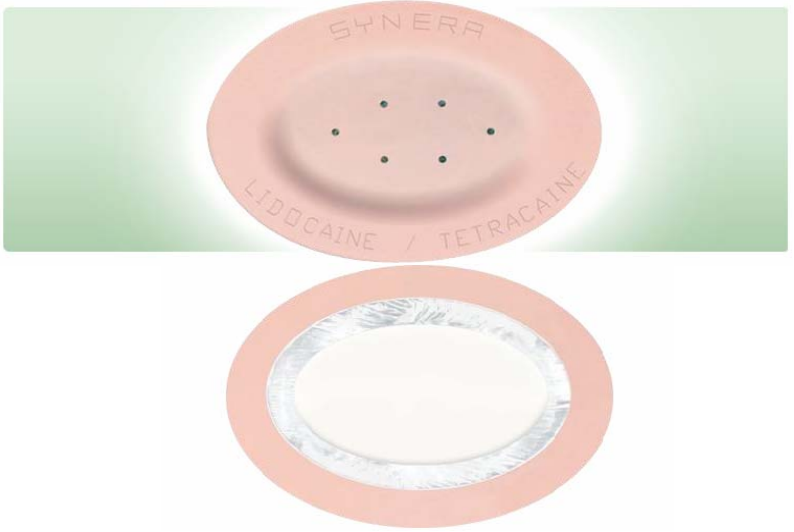
RAPYDAN™ 70mg/70mg
Lidocaine/Tetracaine



Rapydan™ Construction



RAPYDAN

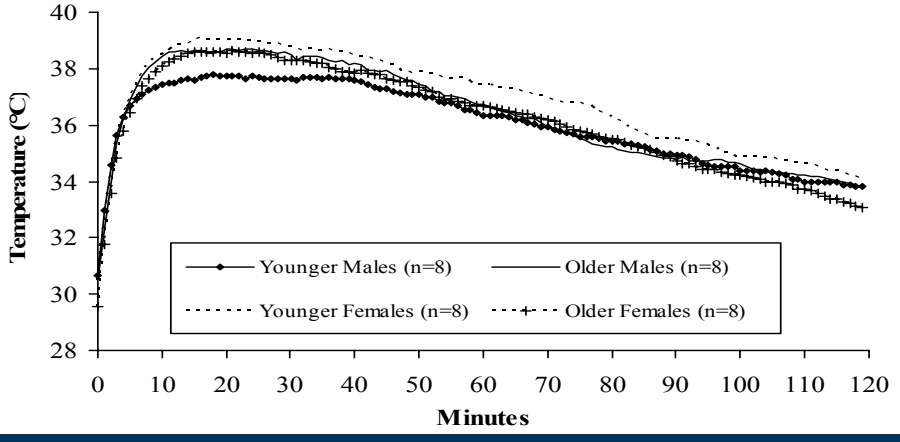


HOW TO USE

- 3 simple steps
  - Apply to intact skin immediately after opening the pouch
  - Leave plaster for 30 minutes
  - Remove and clean site before use
- Dose in Children
  - Up to 2 patches simultaneously
  - 2 patches per 24 hours

RAPYDAN

PATCH HEATING PROFILE



TOXICOLOGY STUDIES

- Acute toxicity
- Dermal sensitization – animal and human
- Repeat-dose toxicity
- Mutagenicity – lidocaine and tetracaine
- Reproductive toxicity

PHARMACOKINETIC STUDIES

- Adult, Geriatric and Pediatric (newborn-adolescence)
- Single dose, repeat-dose, extended application times
  - Simultaneous and sequential patch applications
  - 20, 30 and 60-minute application times
- LLQ 0.9 ng/mL for lidocaine and tetrcaine
- Lidocaine toxicity
  - Lower range 1000 ng/mL
  - 2000-5000 ng/mL used for ventricular arrhythmias
  - >5000 ng/mL associated with AEs in adults

PEDIATRIC PHARMACOKINETICS

- Single dose, repeat dose (simultaneous)
- Plasma sampling 30 min – 24 hours
- Patch application: 30 or 60 minutes
- All tetracaine values < 65 ng/mL (most BLQ)
- Lidocaine: Highest Cmax: 331 ng/mL

PEDIATRIC STUDIES

- Efficacy and Safety Pediatric Studies Completed
- Total of 249 pediatric patients studied - ages 4 months to 17 years
- 43 patients 2 years of age and younger
- Additional PK trial ongoing in neonates and premature infants

SAFETY ENDPOINTS

- Skin assessment immediately following plaster application
- Prospective evaluation for erythema, edema and blanching
- 24-48 post treatment skin evaluation
- ICH guidelines for collection of adverse events

SAFETY ENDPOINTS

- Adhesive safety evaluation in 80 children
< 2 years old
- Skin Sensitization study (RIPT)
  - 4 week exaggerated application
    - 3 applications per week
    - 2 hour application
  - Rest and challenge phases
  - No sign of cumulative irritation
  - No sensitization observed

SAFETY ENDPOINTS

- Most common adverse event was erythema - spontaneous resolution typical
- No Serious Adverse Events

PEDIATRIC EFFICACY STUDIES

- Efficacy Measures
  - Primary:
    - Oucher scale for patient self-report of pain intensity
      - Numerical version
      - Pictoral version
  - Secondary:
    - Physician/independent observer report of patient pain intensity

SC-09-99 Design

- Randomized 1:1, double-blind and placebo controlled (placebo with heat, no drug)
- Parallel
- Screening, patch application (30 min), post tx skin assessment, 23 gauge vascular access procedure, efficacy evaluations, 24-48 hr safety assessment, study termination

SC-09-99 Demographics/Details

- 60 subjects ages 7-17 years enrolled
- Required vascular access procedure
- Evaluated pain using Oucher Numerical scale

SC-09-99 Results

	SC-09-99 (n=60)
Treatment Application Period	30 min
No. Subjects (S-Caine/Placebo)	30/30
Median Oucher Scale Score	N
S-Caine	0
Placebo	35
P-Value	<0.001

P = Photographic, N = Numeric

SC-10-00 Design

- Randomized 1:1, double-blind and placebo controlled (placebo with heat, no drug)
- Parallel
- Screening, patch application (20 min), post tx skin assessment, 23 gauge vascular access procedure, efficacy evaluations, 24-48 hr safety assessment, study termination

SC-10-00 Demographics/Details

- 58 subjects ages 7-17 years enrolled
- Required vascular access procedure
- Evaluated pain using Oucher Numerical scale

SC-10-00 Results

	SC-10-00 (n=60)
Treatment Application Period	20 min
No. Subjects (S-Caine/Placebo)	29/29
Median Oucher Scale Score	N
S-Caine	0
Placebo	20
P-Value	<0.001

P = Photographic, N = Numeric

SC-20-01 Design

- Randomized 2:1, double-blind and placebo controlled (placebo with heat, no drug)
- Parallel
- Stratified by age groups 3-6 and 7-17
- Screening, patch application (20 min), post tx skin assessment, 21 and 22 gauge vascular access procedure in majority of patients, efficacy evaluations, 24-48 hr safety assessment, study termination

SC-20-01 Demographics/Details

- 31 subjects ages 3-6
- 30 subjects ages 7-17
- Required vascular access procedure
- Additional cognitive evaluation completed to determine use of numerical or pictoral Oucher
  - Subsequent uneven distribution

SC-20-01 Results

	SC-20-01 (n= 61)	
Treatment Application Period	20 min	
No. Subjects (S-Caine/Placebo)	25/11	16/9
Median Oucher Scale Score	P	N
S-Caine	0	7.5
Placebo	80	50
P-Value	<0.001	0.159

P = Photographic, N = Numeric

SC-20-01 Results Discussion

- 31 subjects ages 3-6
- 30 subjects ages 7-17
- Required vascular access procedure
- Additional cognitive evaluation completed to determine use of numerical or pictoral Oucher
  - Subsequent uneven distribution

VASCULAR ACCESS STUDIES IN PEDIATRICS

	SC-09-99 (n=60)	SC-10-00 (n=60)	SC-20-01 (n= 61)	
Treatment Application Period	30 min	20 min	20 min	
No. Subjects (S-Caine/Placebo)	30/30	29/29	25/11	16/9
Median Oucher Scale Score	N	N	P	N
S-Caine	0	0	0	7.5
Placebo	35	20	80	50
P-Value	<0.001	<0.001	<0.001	0.159

P = Photographic, N = Numeric

IMPACT OF HEAT ON EFFICACY

- Randomized, double-blind, parallel design study
- Designed to document the impact of heat on the effectiveness of Rapydan
- 250 adult volunteers, each studied once

IMPACT OF HEAT ON EFFICACY

- Subjects received either Rapydan with heating element or Rapydan with heating element removed
  - Patches applied to right antecubital surface for 20 minutes
  - Patients then underwent IV cannulation using a 16-guage catheter
    - Pain intensity (VAS) and other efficacy measures obtained

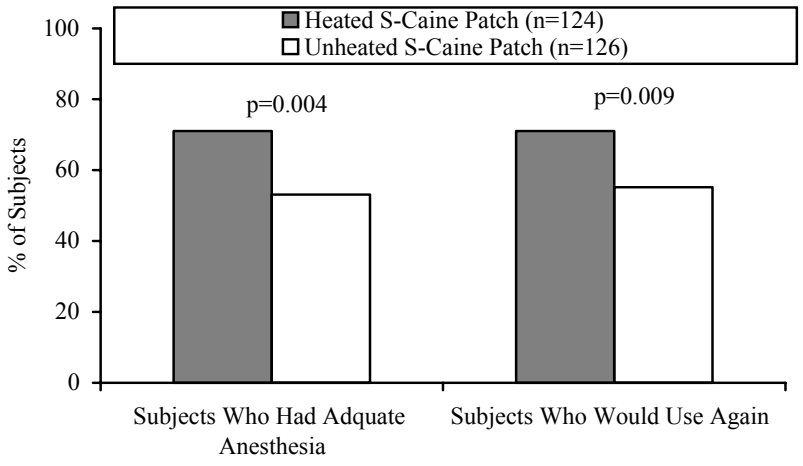
IMPACT OF HEAT ON EFFICACY

Visual Analog Scale Scores by Treatment Group (N=250)

Statistic	Heated S-Caine Patch (n=124)	Unheated S-Caine Patch (n=126)	p-value (two-sided)
Mean	22.1	28.7	
SD	20.7	22.8	
Median	16.5	22	
Geometric Mean[b]	14.2	20.5	0.006[a]
Minimum	0	0	
Maximum	97	95	

[a]two-sample t-test
[b]antilog of the mean of log (VAS+1)

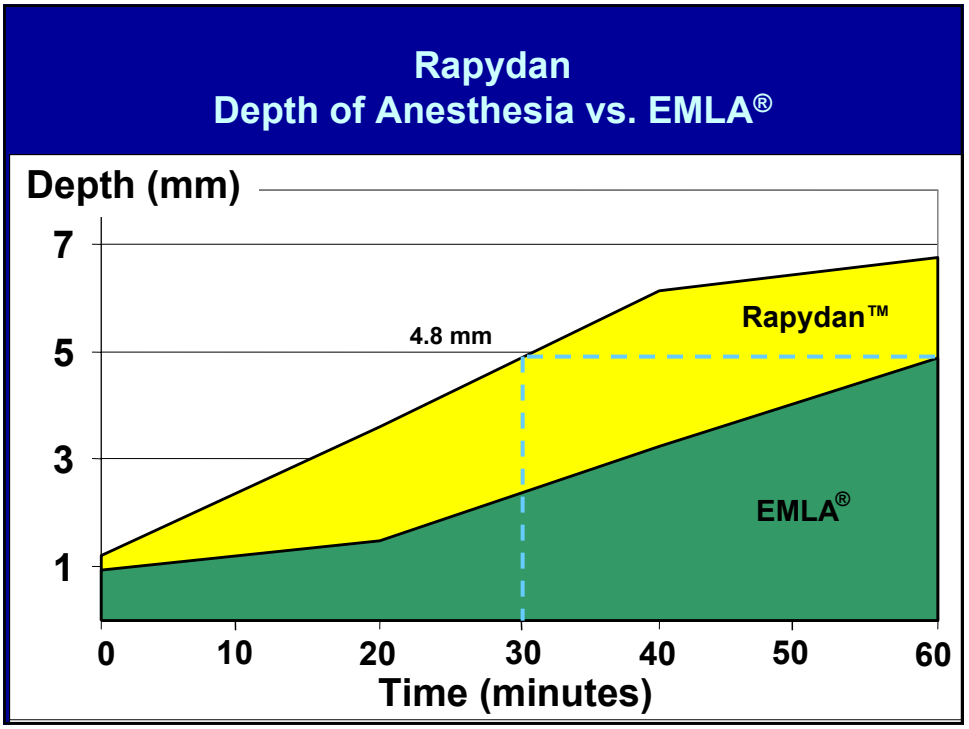
IMPACT OF HEAT ON EFFICACY



RAPYDAN and EMLA Comparative Trials

First pilot study

- 12 adult volunteers
- Paired study
- Application times of 20, 40 and 60 minutes
- Needle gauge with calipers
- ZARS' recreation of Medieval Research!



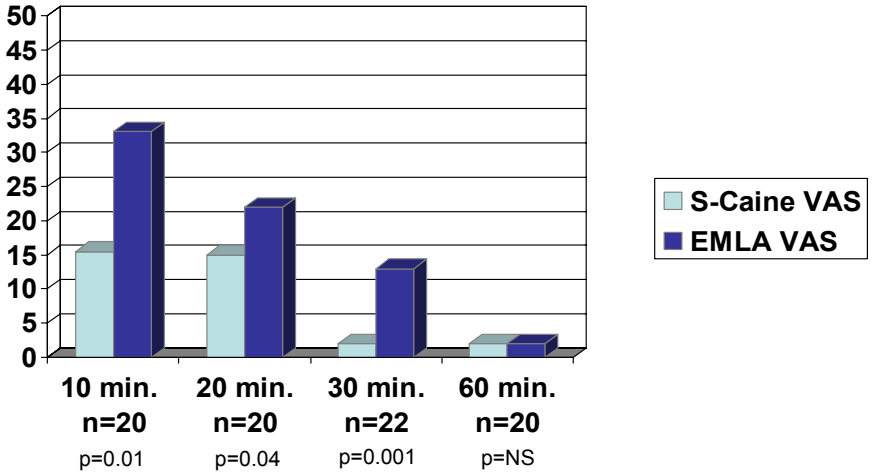
Depth of Anesthesia vs EMLA

Time Point	p-value
Baseline	Not Significant
20 minutes	0.0556
40 minutes	0.0073
60 minutes	Not Significant
Base/20/40/60	0.0002

RAPYDAN and EMLA Comparative Trials

- Pivotal trial
  - Randomized, double-blind, EMLA comparative in 82 healthy adult volunteers
  - Single center, UK
  - Vascular access procedures
  - 4 application time cohorts
    - 10, 20, 30 and 60 minutes
  - Primary efficacy endpoint:
    - Patient pain intensity as measured by VAS

COMPARISON AGAINST EMLA



COMPARISON AGAINST EMLA

	10 minutes	20 minutes	30 minutes	60 minutes
% reporting anesthetic eliminated pain				
S-Caine Patch	65%	90%	95%	95%
EMLA Cream	42%	60%	64%	95%
p-value	0.059	0.014	0.020	1.000
% who would use anesthetic again				
S-Caine Patch	80%	95%	100%	90%
EMLA Cream	47%	70%	64%	95%
p-value	0.008	0.014	0.005	0.317

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Rapydan:
Introduction of a new option in topical anaesthesia

Questions?