St. Jude
PMVOC ID# NCT01954927
Initial version, dated: 02-28-2013, (IRB Approved: 06-25-13) Activation date 00-00-00
Amendment 1.0, dated 08-16-13 (IRB Approved: 09-24-13) Activated: 10-07-13
Amendment 2.0, dated 03-28-2014 (IRB Approved: 05-13-14) Activated: 05-21-14
Revision 2.1, dated 6-19-14 (IRB Approved: 07-19-14) Activated: 07-24-14
Amendment 3.0, dated 12-02-2014 (IRB Approved: 02-24-2015) Activated: 03-30-2015
Revision 3.1, dated 1-25-16
Un-numbered Revision, dated: 08-28-2017 (IRB Approved: 09-15-2017)
Revision 3.2, dated: 10-12-2017, (IRB Approved: 11-16-2017)
Un-numbered Revision, dated: 06-20-2018 (IRB Approved: 07-02-2018)

PAIN MANAGEMENT OF VASO-OCCLUSIVE CRISIS IN CHILDREN AND YOUNG ADULTS WITH SICKLE CELL DISEASE

IND/IDE # 119125

Principal Investigator:
Doralina Anghelescu, MD
Division of Anesthesiology

Co-Investigators:
Jane Hankins, MD[1]
Latika Puri, MD[1]
Guolian Kang, PhD[3]
Chen Li[3]

[1]Department of Hematology
[2]Division of Anesthesiology
[3]Department of Biostatistics

St. Jude Children's Research Hospital
262 Danny Thomas Place
Memphis, Tennessee 38105-3678
Telephone: (901) 595-3300

PMVOC - Pain Management of Vaso-occlusive Crisis in Children and Young Adults with Sickle Cell Disease
Principal Investigators: Doralina Anghelescu, MD and Kerri Nottage, MD
IND Holder: St. Jude Children's Research Hospital, # 119125
Brief Overview: This is a phase II double-blind placebo-controlled clinical trial evaluating the effect of gabapentin when added to standard pain management for patients with sickle cell disease experiencing acute pain crisis in the ambulatory care setting. Patients will be randomized to receive a single oral dose of gabapentin or placebo as soon as feasible after enrollment. Pain scores and opioid requirement will be measured and compared across treatment arms, along with the outcomes of discharge from clinic versus admission to the inpatient unit.
Intervention: Gabapentin 15mg/kg vs placebo (single dose by mouth)
Brief Outline of Treatment Plan: Participants will receive a single dose of study drug by mouth as soon as feasible after enrollment, while standard pain management is provided concurrently. The remainder of care for the painful event will continue per institutional standards according to clinical indication, including reassessment and documentation of pain and additional doses of pain medicines by IV or oral route. Treating clinicians will determine if the patient may be discharged home or if admission is warranted.
Study Design: Phase II double-blind placebo-controlled therapeutic trial.
Sample Size: 166 participants divided evenly between active and placebo arms.
Data Management: Data management and statistical analysis will be provided locally by the Anesthesia Division and Biostatistics Department at St. Jude Children's Research Hospital
Human Subjects: The risks to subject will be related to the toxicity of gabapentin. The expected side effect is somnolence. Patients will be informed of this and other minor side effects during informed consent discussion. Adverse events will be monitored and reported and treated appropriately.

Table of Contents

1.0 OBJECTIVES

1.1 Primary Objective

To assess the analgesic efficacy of gabapentin (vs. placebo) for pain during vaso-occlusive crisis (VOC) in participants with sickle cell disease (SCD). A response to study drug will be defined by a decrease in pain score of ≥33% between presentation to the acute care setting and assessment at 3 hours post administration of study drug.

1.2 Secondary Objective

To compare the total morphine equivalent dose (mg/kg) used to control pain during VOC between presentation to the acute care setting and assessment at 3 hours post administration of study drug in the gabapentin vs. placebo groups.

1.3 Exploratory Objectives

1.3.1 To assess the analgesic efficacy of gabapentin (vs. placebo) for pain during VOC in participants with SCD, as defined by a decrease in pain scores of ≥33% between presentation to the acute care setting and the point of decision for either hospital admission or discharge to home, in the gabapentin and placebo groups.

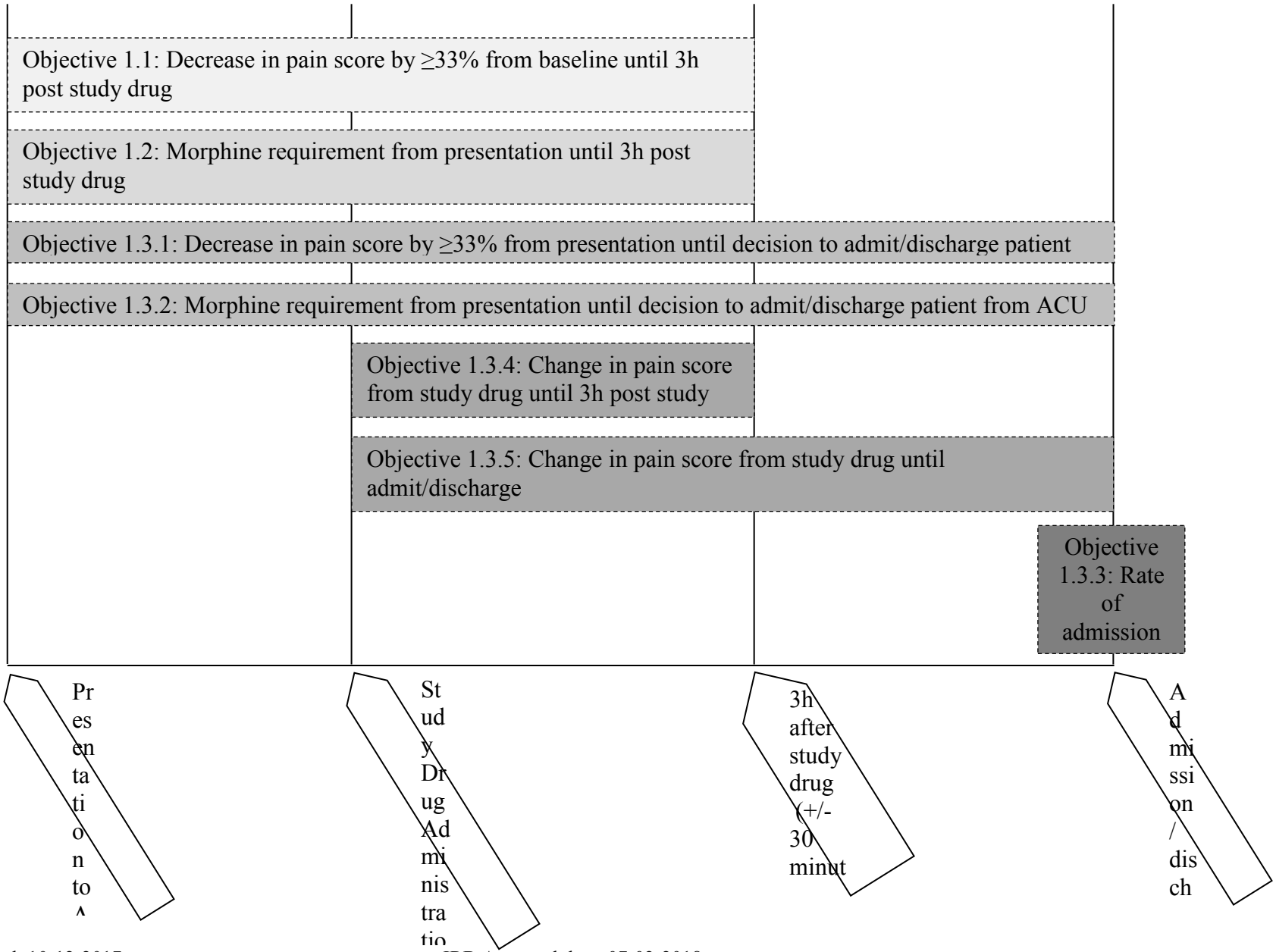
1.3.2 To compare the total morphine equivalent dose (mg/kg) used to control pain during VOC between presentation to the acute care setting and the point of decision for either admission or discharge to home, in the gabapentin and placebo groups.

1.3.3 To compare the rate of admission related to pain management, in the gabapentin vs. placebo groups.

1.3.4 To compare the change in pain score from time of administration of study drug to assessment at 3 hours post administration of study drug in the gabapentin vs. placebo groups.

1.3.5 To compare the change in pain score from time of administration of study drug to the point of decision for either admission or discharge to home, in the gabapentin and placebo groups.

Figure 1. Pain Assessment Time Points and Study Objectives



2.0 BACKGROUND AND RATIONALE

2.1 Background:

Gabapentin has been used successfully to treat neuropathic pain [1-3], and nociceptive pain [4]. The mechanism of action is binding of the α-2-δ subunits of the voltage-dependent calcium ion channels, which blocks the development of hyperalgesia and central sensitization [5, 6]. The reasons for the effectiveness of gabapentin for nociceptive pain are based on several considerations:

1. Gabapentin has been shown to prevent central sensitization, manifested as hyperalgesia, a known phenomenon in postoperative pain [7]. The mechanism for reduction of central sensitization is the reduction of hyperexcitability of secondary nociceptive neurons in the dorsal horn, through suppressing the release of excitatory amino acids in the spinal cord in response to noxious stimuli [8].

2. Gabapentin and morphine may be synergistic due to separate actions on the peripheral and central nervous system [9].

3. Gabapentin may decrease the postoperative morphine requirement by preventing the development of opioid tolerance [10].

Sixteen randomized controlled trials were included in a systematic review of gabapentin use for postoperative pain [4].

Among three different gabapentin regimens including a single dose of 1200 mg preoperatively, a <1200 mg single dose preoperatively, multiple doses perioperatively (both preoperatively and postoperatively), the regimens of single doses of 1200 mg or less were found effective by two measures of analgesic efficacy: 1) reduced pain intensity scores, and 2) reduced opioid consumption for the first 24 hours postoperatively. The single dose regimen of 1200 mg also prolonged the time to first request for rescue analgesia with opioid.

In a randomized controlled study of gabapentin 15 mg/kg single dose versus placebo in children aged 9 to 18 years undergoing spinal fusion surgery, the investigators found a significant decrease in the total morphine consumption in the gabapentin group, in the recovery room, and at postoperative day 1 and 2 [11]. The pain scores were also significantly decreased in the gabapentin group in the

recovery room and at postoperative day 1. In this study, gabapentin versus placebo was administered postoperatively for 5 days, at doses of 5 mg/kg TID; the analgesic benefit of gabapentin was only found for the first 2 days postoperatively based on diminished opioid consumption and only for the first postoperative day based on both decreased opioid consumption and decreased pain scores. The authors concluded that perioperative use of gabapentin seems to be an effective adjunct to improve pain control and is recommended as an initial loading dose of gabapentin and continued treatment for 2 days after spinal fusion surgery.

The current algorithms for management of pain associated with VOC in SCD are not satisfactory. The most effective pain treatment should intervene early in the course of a VOC, in the prodromal phase; early intervention could prevent or minimize tissue damage [12]. If we can demonstrate that a therapeutic intervention with a single dose of gabapentin can provide analgesic efficacy, this drug could be utilized as an early intervention, which can be initiated at home, in the prodromal phase of a VOC.

In addition to ample evidence of efficacy for management of neuropathic pain, gabapentin has proven opioid-sparing effects in an acute pain setting, that of acute postoperative pain, in adults [13, 14] and children [11]. The regimen applied in the pediatric postoperative setting, in children 9 to 18 years, was gabapentin 15 mg/kg versus placebo, given preoperatively. After surgery, the regimen continued as 5 mg/kg or placebo 3 times a day for 5 days. This regimen of an initial preoperative loading dose and continued oral gabapentin postoperatively decreased the total morphine consumption and pain scores up to 2 days postoperatively, but no benefit was demonstrated beyond 2 days.

Additional Literature review of gabapentin for acute postoperative pain

Cochrane review

A Cochrane review has evaluated the single oral dose, randomized, double-blind, placebo-controlled trials of gabapentin for relief of established moderate to severe postoperative pain in adults (>15 yrs) [15]; the dose evaluated in the review was a 250 mg single dose administered preoperatively. Studies were assessed for methodological quality and data extracted by two review authors independently. Numbers of participants with at least 50% of maximum possible total pain relief (TOTPAR) or summed pain intensity difference (SPID) with gabapentin or placebo were calculated and used to derive relative benefit (RB) or risk (RR), and number-needed-to-treat-to-benefit (NNT). Numbers of participants using rescue

medication, and time to its use, were sought as additional measures of efficacy. Information on adverse events and withdrawals was collected. Four unpublished studies met inclusion criteria; in three, participants had pain following dental surgery, and one followed major orthopedic surgery; 177 participants were treated with a single dose of gabapentin 250 mg, 21 with gabapentin 500 mg, and 172 with placebo. At least 50% pain relief over 6 hours was achieved by 15% with gabapentin 250 mg and 5% with placebo; giving a RB of 2.5 (95% CI 1.2 to 5.0) and an NNT of 11 (6.4 to 35). Significantly fewer participants needed rescue medication within 6 hours with gabapentin 250 mg than with placebo; NNT to prevent use 5.8. About one third of participants reported adverse events with both gabapentin 250 mg and placebo. No serious adverse events occurred with gabapentin. The authors' conclusions were that gabapentin 250 mg is statistically superior to placebo in the treatment of established acute postoperative pain, but the NNT of 11 for at least 50% pain relief over 6 hours with gabapentin 250 mg is of limited clinical value and inferior to commonly used analgesics. Gabapentin 250 mg is not clinically useful as a stand-alone analgesic in established acute postoperative pain, though this is probably the first demonstration of analgesic effect of an antiepileptic in established acute pain.

Table 1. Summary of results of gabapentin for surgical pain presented by Straube, et al in a Cochrane Review, 2010, page 8 [15]

Summary of results: gabapentin 250 mg versus placebo				
Outcome	**Studies**	**Gabapentin (%)**	**Placebo (%)**	**Summary statistic**
Number of participants with ≥50% pain relief over 6 hours	3	15	5	NNT: 11 (6.4 to 35)
Number of participants using rescue medication over 6 hours	3	68	86	NNTp: 5.8 (3.8 to 12)
Number of participants with ≥1 adverse event	3	28	32	NNH: not calculated

Based on the evidence that low dose gabapentin (250 mg, approximately 3-5mg/kg in adults) has limited efficacy, we propose a higher dose regimen in our study intervention, at 15 mg/kg, maximum 900 mg.

Meta-analyses and systematic reviews

Three meta-analyses [16-18] and one systematic review [4] provide reviews of placebo controlled RCTs of the use of gabapentin for perioperative pain control in adults. The systematic review [4] included 16 RCTs in the analysis. A total of 1151 patients were studied, of whom 614 patients received gabapentin. Gabapentin was given as a single preoperative dose in 11 [13, 19-27], as two separate preoperative doses in 1 [28], and as more than two doses in the perioperative period in four clinical trials [14, 29-31]. The dosages of gabapentin administered ranged between 300 and 1200 mg. To facilitate quantitative analysis, three subgroups were created: (i) group receiving single dose of gabapentin 1200 mg preoperatively; (ii) group receiving single dose of gabapentin less than 1200 mg preoperatively; and (iii) group receiving multiple doses of gabapentin in the perioperative period. Pain intensity, total analgesic consumption and time to first request for rescue analgesia were analyzed separately in each subgroup.

Eight trials used a single preoperative dose of 1200 mg gabapentin in the treatment group [13, 19, 22, 24-27, 32] Combined data on pain intensity in six studies [13, 21, 22, 25-27, 32] showed a significant decrease in pain intensity at rest with gabapentin compared with control in the early by weighted mean differences (WMD, -16.55 mm; 95% CI -25.66 to -7.44) and late (WMD, -10.87 mm; 95% CI -20.90 to -0.84) postoperative period at 6 and 24 h, respectively. Combined data from three studies that reported on opioid consumption at 24 h [13, 22, 24] showed that the WMD of -27.9 mg (95% CI -31.52 to -24.29) was in favor of gabapentin. Meta-analysis of the two studies with data on the time to first request for rescue analgesic [13, 32] showed that gabapentin produced a statistically significant delay in time to first request for analgesia (WMD 7.42 min; 95% CI 0.49–14.34).

Five studies with seven treatment arms used a single preoperative dose of gabapentin that was less than1200 mg [20-23, 27]. The dose range was between 300 and 900 mg. Combined data from all five RCTs showed a statistically significant decrease in pain intensity at rest with gabapentin compared with control in the early postoperative period at 6 h (WMD, -22.43 mm; 95% CI -27.66 to -17.19). Combined data from four RCTs [20-23] showed lower pain scores at rest in the gabapentin group in the late postoperative period at 24 h (WMD, -13.18 mm; 95% CI -19.68 to -6.68). Combined data from four RCTs [20-23] showed that gabapentin reduced postoperative morphine consumption compared with control (WMD, -15.98 mg; 95% CI -23.45 to -8.50). None of the five studies measured time to first analgesia as an outcome.

Five studies reported gabapentin given as multiple doses perioperatively. Gabapentin was administered as follows in these five studies: 1) two separate 400 mg doses preoperatively [28]; 2) 600 mg 1 h preoperatively and then three times a day for 24 h postoperatively [30]; 3)1200 mg of gabapentin before surgery followed by 600 mg 8 hourly for an additional three doses [29]; 4) 400 mg gabapentin the night before surgery and then 400 mg three times a day for 10 days [14]; and 5)1200 mg gabapentin preoperatively, followed by 1200 mg on the morning of the first and second postoperative day [31]. Only two out of the five trials had data suitable for meta-analysis for the pain intensity outcome measure [14, 30]; the combined data did not show any difference between gabapentin and control groups at both 6 and 24 h after surgery. Only one study measured 24 h morphine consumption as an outcome [31]: it showed a 24% reduction in total patient-controlled analgesia morphine usage in the gabapentin group compared with the control group. Only one study presented the time to first request for rescue analgesic data as an outcome and reported no difference between the gabapentin and control groups [14].

This systematic review demonstrated that preoperative gabapentin administration was useful for postoperative pain management. A single preoperative dose of gabapentin, 1200 mg or less, effectively reduced pain intensity and opioid consumption for the first 24 h after surgery. In the subgroup that received a single 1200 mg of gabapentin preoperatively, the time to first request for rescue analgesia was also prolonged. However, multiple dosing with gabapentin preoperatively and continued postoperatively did not appear to reduce VAS pain scores.

This systematic review therefore demonstrates a potential role for preemptive gabapentin as an adjunct to standard postoperative pain management. In the groups receiving a single dose of gabapentin preoperatively, the reduction in pain scores appeared to be more pronounced in the early postoperative period. However, this reduction was still significant at 24 h and was
associated with a significant reduction in opioid consumption.

The conclusion of the systematic review was that perioperative administration of gabapentin is effective in reducing pain scores, opioid requirements and opioid-related adverse effects in the first 24 h after surgery. Sedation was associated with its use but no serious adverse effects were observed.

One meta-analysis [18] evaluated eighteen studies [13, 14, 19-34] encompassing 1181 patients; mean ages ranged from 29 to 52 years of age. The most common

dose of gabapentin assessed was1200 mg daily (12 studies), with some studies using doses as low as 300 mg daily (Table 2). Eleven studies [13, 19-27, 32] administered gabapentin as a single dose within 1 h to 2 h before surgery; the remainder involved initiating therapy on the day before surgery or continuing it for up to 10 days after surgery (Table 2). Gabapentin caused a significant reduction in postoperative pain at rest [13, 14, 19-31, 33, 34] in the first 24 h, by 27% to 39% (7.2 mm to 14.3 mm on a scale of 0 mm to 100 mm), regardless of whether treatment effects were expressed as ratios of means or weighted mean differences. Similarly, aside from 24 h after surgery, gabapentin significantly reduced pain with movement [13, 14, 19, 20, 25, 28-30, 33] by 18% to 28% (VAS 8.2 mm to 10.2 mm) after surgery. Fourteen studies [14, 19, 20, 22, 23, 25-27, 33], encompassing 1027 participants, reported effects on cumulative 24 h analgesic consumption. Gabapentin resulted in a 35% reduction in total analgesic consumption over the first 24 h following surgery (ratio of means 0.65, 95% CI 0.59 to 0.72; P<0.001), albeit with significant heterogeneity (I2=84.4%). The data on time to first analgesic was available in three studies [13, 24, 32], (171 patients); it was delayed 7.9 min by gabapentin (95% CI 4.2 to 11.6; P<0.001), with minimal heterogeneity (I2=0%).

This meta-analysis concluded that perioperative administration of gabapentin reduces pain scores, both at rest and with movement following various surgeries, lengthens the time for analgesic rescue, decreases the consumption of opioids and lowers rates of opioid-related side effects. The pain score at rest was reduced by 27% to 39% (VAS 7.2 mm to 14.3 mm on a
scale of 0 mm to 100 mm) during the first 24 h, and the pain score with movement was reduced by 18% to 28% (VAS 8.2 mm to 10.2 mm) in the first 12 h.

The two meta-analyses on the topic of perioperative use of gabapentin published prior to Peng's meta-analysis of 18 studies were less extensive and included only eight [16], and 12 [17] studies, respectively; therefore they are not included in this literature review.

The evidence of effectiveness of gabapentin as an adjunct to reduce acute postoperative pain has further generated the question of whether gabapentin would also be effective in preventing chronic post-surgical pain. A recent combined systematic review and meta-analysis reviewed the effectiveness of gabapentin and pregabalin in the perioperative period for the prevention of chronic post-surgical pain [35] and concluded that perioperative administration of gabapentin and pregabalin is effective in reducing the long-term incidence of chronic post-surgical pain.

Table 2. Characteristics of the studies included in the Peng (2007) meta-analysis

Study	Procedure	n	Treatment arm	Control arm	Anesthesia
Gynecological procedures					
Dierking et al (34)	Abdominal hysterectomy	80	Gabapentin 1200 mg 1 h before surgery, and 600 mg 8 h, 16 h and 24 h after initial dose	Placebo	General
Gilron et al (35)	Abdominal hysterectomy	52	Gabapentin 1800 mg daily starting 1 h before surgery to postoperative day 2	Placebo	General
Rorarius et al [32]	Vaginal hysterectomy	90	Gabapentin 1200 mg 150 min before surgery	Oxazepam 15 mg	General
Turan et al [25]	Abdominal hysterectomy	50	Gabapentin 1200 mg 1 h before surgery	Placebo	General
Turan et al [34]*	Abdominal hysterectomy	50	Gabapentin 1200 mg daily starting 1 h before surgery to postoperative day 2	Placebo	General
Yoon et al [33]	Abdominal hysterectomy	32	Gabapentin 800 mg before surgery (400 mg the night before surgery and 400 mg 30 min before surgery)	Placebo	General
Orthopedic procedures					
Menigaux et al [13]	Knee surgery	40	Gabapentin 1200 mg 2 h before surgery	Placebo	General
Pandey et al [21]	Spine surgery	56	Gabapentin 300 mg 2 h before surgery	Placebo	General
Pandey et al [22]	Spine surgery	100	Any of four doses of gabapentin (300 mg, 600 mg, 900 mg or 1200 mg) 1 h before surgery	Placebo	General
Radhakrishnan et al [28]	Spine surgery	60	Gabapentin 800 mg before surgery (400 mg the night before surgery and 400 mg 2 h before surgery)	Placebo	General
Tuncer et al [27]	Major orthopedic surgery	45	Any of two doses of gabapentin (800 mg or 1200 mg) 1 h before surgery	Placebo	General
Turan et al [24]	Spine surgery	50	Gabapentin 1200 mg 1 h before surgery	Placebo	General
Turan et al [31]	Lower limb surgery	40	Gabapentin 1200 mg daily starting 1 h before surgery to postoperative day 2	Placebo	General & epidural
Other procedures					
Dirks et al [19]	Breast surgery	70	Gabapentin 1200 mg 1 h before surgery	Placebo	General
Fassoulaki et al [14]†	Breast surgery	50	Gabapentin 1200 mg daily starting evening before surgery to postoperative day 10	Placebo	General
Pandey et al [20]	Laparoscopic cholecystectomy	206	Gabapentin 300 mg 1 h to 2 h before surgery	Placebo	General
Pandey et al [23]	Open nephrectomy	60	Gabapentin 600 mg either 2 h before surgery or following surgical incision.		
Turan et al [26]	Ear-nose-throat surgery	50	Gabapentin 1200 mg 1 h before surgery	Placebo	Sedation

*Additional two arms that assessed celecoxib (alone and in conjunction with gabapentin) were excluded; †Additional arm that assessed mexilitene was excluded

Other RCTs of gabapentin in the perioperative period (2010-2013)

Clinical studies with a RCT design, published recently (2010-2013) and not included in any previous meta-analyses or systematic reviews, are presented in Table 3. Of 20 RCTs, 16 found a positive outcome for at least one outcome measure, while 4 studies had negative or inconclusive results. The only pediatric study [11] is also included in Table 3.

Based on the comprehensive literature review, which is suggestive of the efficacy of gabapentin for nociceptive acute postoperative pain, we propose that the nociceptive pain encountered in the VOC crisis could also be responsive to the addition of gabapentin to the other two classes of medications representing the current standard of care, opioids and non-steroidal anti-inflammatory drugs.

Based on evidence that a single dose regimen has better analgesic efficacy than multi-dose regimens, we proposed a single dose of gabapentin of 15mg/kg, maximum 900mg.

Table 3. Randomized Controlled Trials investigating gabapentin for surgical pain, 2010 – 2013.

Author, Year [Reference]	n (analyzed)	Population	Intervention	Outcome measure	Results	
Paul, 2013 [36]	101	Total Knee Arthroplasty, adults	PBO vs Gaba 600mg preop + 200mg q8h x2d	Cumulative morphine consumption at 72h; pain scores and pt satisfaction	-	No effect on morphine consumption; No effect on pain scores or pt satisfaction
Clarke, 2013 [37]	50 (44)	Adult females with anxiety + surgery	PBO vs Gaba 1200 preop	Reduction in preop anxiety	+	gabapentin prior to surgery reduces preoperative anxiety scores and pain catastrophizing scores and increases sedation prior to entering the operating room.
Lee, 2013 [38]	80 (71)	Elective thyroid surgery, adults	PBO vs Gaba 600mg preop	Reduction of incidence of postop sore throat at rest and during swallow; Reduction of intensity of postop sore throat at rest and during swallow	+	gaba reduced sore throat incidence and intensity at rest, but not during swallow.
Short, 2012 [39]	132 (126)	Elective cesarean delivery, adult women	PBO vs Gaba 600mg preop vs Gaba 300mg preop	Pain on movement at 24h; pt satisfaction, supplimental opioid, other endpoints related to childbearing	none	Results did not reach statistical significance, insufficient power to detect difference
Adam, 2012 [40]	64	Surgery under GA, adults	PBO vs Gaba 1200mg	Reduction of preop anxiety; preop sedation without amnesia	+	Statistically significant decrease of one anxiety measure, decrease (not stat sig) of second anxiety measure. No significant differences in sedation or memory or pt satisfaction
Ajori, 2012 [41]	170 (130)	Abdominal hysterectomy, adult women	PBO vs Gaba 600mg preop	Reduction of postop pain; opioid, antiemetic consumption at 24h	+	Significant decreases in all measures.
Kinney, 2012 [36]	120	elective thoracotomy, adults	active PBO vs Gaba 600mg preop	Pain scores, opioid consumption, side effects x48h	-	No analgesic benefit
Behdad, 2012 [42]	61	Abdominal hysterectomy, adult women	PBO vs Gaba (100mg 1 day prior, 300mg 2h preop)	Pain, nausea, vomiting, vitals, morphine use	+	Except in the first hour after operation ($p = 0.02$), there was no significant differences between the two groups in morphine use.

Author, Year [Reference]	n (analyzed)	Population	Intervention	Outcome measure	Results	
Deniz, 2012 [43]	51	Radical retropubic protatectomy, adult males	Gaba 900mg preop vs none	Opioid consumption, pain scores, rescue analgesia	+	Lower pain scores and reduced rescue analgesia; no difference in opioid consumption.
Ozgencil, 2011 [44]	90	laminectomy and discectomy, adults	PBO vs Gaba 600 vs Pregaba 150mg q12h x2 preop	morphine consumption, pain scores, preop anxiety, pt satisfaction	+	Both gaba and pregaba showed significant positive effects in all measurement categories.
Panah- Khahi, 2011[45]	64	Lower extremity orthopedic surgery, adults	PBO vs 300mg Gaba preop	Pain scores, time to rescue opioid, total opioid consumption	+	Pain scores significantly lower at 2h, no differences later.
Ucak, 2011 [46]	40	CABG, adults	PBO vs Gaba 1200 preop and x2d	pain (at rest and coughing), tramadol use	+	Gabapentin significantly reduced the intensity of pain and tramadol consumption in the early postoperative period after CABG surgery. Pain scores at 1 and 3 months after surgery were low in both groups, with no significant difference between the groups.
Spence, 2011 [47]	70	Shoulder arthroscopy, adults	PBO vs Gaba 300mg preop then BID x2d	Average pain scores; opioid consumption, AE, sleep	-	No analgesic benefit
Ghai, 2011 [48]	90	Abdominal hysterectomy, adult women	PBO vs Gaba 900 vs 300 Pregaba preop	Analgesic consumption x24h; pain scores, time to rescue analgesia	+	Significantly lower analgesic consumption for both Gaba and Pregaba vs placebo; Pain scores lower for first hour then no differences; rescue analgesia time lowest for pregaba then gaba then PBO.
Khan, 2011 [49]	175	lumbar laminectomy, adults	7 groups: 600, 900, 1200mg gaba preop vs postop vs PBO	Morphine consumption, time to rescue analgesia, pain scores	+	Gabapentin 900 or 1200 mg, administered either pre- or post-incision, was found to be effective in pain management following lumbar laminectomy. Similar doses of gabapentin provide he same post-operative analgesia whether administered pre- or post-incision.
Moore, 2011 [50]	46 (44)	Cesarean delivery, adult women	PBO vs Gaba 600mg	Pain scores, satisfaction, opioid consumption, side effects; neonatal interventions	+	Preoperative gabapentin 600 mg in the setting of multimodal analgesia reduces postcesarean delivery pain and increases maternal satisfaction in comparison with placebo. Opioid consumption did not differ.

Author, Year [Reference]	n (analyzed)	Population	Intervention	Outcome measure	Results	
Syal, 2010 [51]	120	Open cholycystectomy, adults	4 groups: PBO, APAP 1000mg, Gaba 1200mg, APAP + Gaba; administered preop	Rescue analgesic (time, number, and total amount); pain score (rest and mvmt)	+	Group 3 had lower pain scores at rest and on movement at all time intervals in comparison to the Group 1. Similarly Group 4 had lower pain scores at rest and on movement at all time intervals in comparison to the Placebo Group. Patients who consumed Gabapentin alone had lower scores at all time intervals in comparison to Group 2 but the difference in resting score was statistically significant only at 0, 1, 2 and 24 hours post-operatively while movement score was statistically significant at all time intervals except at 6 hours
Bang, 2010 [52]	46	Arthroscopic rotator cuff repair, adults	PBO vs Gaba 200mg preop	Pain scores; opioid consumption and side effects	+	Significant decrease in pain scores, no difference in opioid consumption
Amr, 2010 [53]	150	Partial or radical mastectomy, adult women	PBO vs Gaba 300mg/d vs venlafaxine 37.5 mg/d	Pain scores, analgesic requirements	+	Pain after movement was reduced by gabapentin from the second to tenth postoperative day but no difference was found regarding pain during rest. Gabapentin reduced morphine consumed in the first 24 hours postoperatively. The analgesic requirements from the second to tenth days were reduced compared to the control group.
Rapchuk, 2010 [54]	60	Cardiac surgery, adults	PBO vs Gaba 1200mg preop and 600mg BID x2d	Postop opioid, pain, sleep, pt satisfaction	none	No differences
Rusy, 2010 [11]	59	Spinal fusion, Pediatric	PBO vs Gaba 15mg/kg preop and 5mg/kg TID	total morphine consumption, pain scores	+	Significantly less morphine used, reduced pain scores initially.

There is emerging evidence that patients with SCD experience neuropathic pain as a component of their acute pain episodes. Allodynia and hyperalgesia are symptoms commonly experienced by patients with SCD and are defining characteristics of neuropathic pain [55]. In one survey of adult patients seen at a SCD specialty clinic, 90% of 145 patients verbalized pain descriptors consistent with neuropathic pain [56]. Another evaluation of 56 SCD patients age ≥14 years revealed that 40% experienced definite or probable neuropathic pain. Only 4% of patients were receiving treatment directed at neuropathic pain [57]. No formal studies have been completed using gabapentin in patients with SCD.

Based on the evidence suggesting that patients with SCD experience neuropathic pain, the analgesic benefit of gabapentin demonstrated in the acute pain setting, and the limited length of time that patients stay in the acute care setting for pain management for VOC, we propose an intervention consisting of a single dose gabapentin of 15 mg/kg, as soon as possible after presentation to the hospital, in addition to the current standard of practice which includes the use of an opioid and a non-steroidal anti-inflammatory drug for pain in VOC.

Age-appropriate pain assessment tools are used in our institution as per the pain standard of care: the Faces, Legs, Arms, Cry and Consolability (FLACC) pain scale for children younger than 4 years [58], Wong Baker FACES for children 4 to 6 years [59, 60], and NRS for those 7 years or older [61, 62].
The FLACC scale is a 5 item scale that raters use to score each of the 5 categories: F (faces), L (legs), A (activity), C (cry), and C (consolability), which are scores from 0 to 2 (Merkel 1997). The reliability and validity data on the FLACC tool are extensive [58, 63-65].

The Wong Baker FACES is a horizontal scale of 6 hand-drawn faces, now scored from 0 to 10, that range from a smiling “no hurt” face on the left to a crying “hurts worst” face on the right [60]; faces pain scales have been used in numerous to measure acute, procedural and recurrent pain, as reported in a systematic review of faces scales for the self-report of pain intensity in children[66]. The Wong Baker FACES has adequate psychometric properties, and it is easy and quick to use [60, 66, 67] and inexpensive to reproduce. The greatest strength of this is its acceptability; studies have consistently found that the WBFPRS was preferred by children of all ages, parents, and practitioners, when compared with other faces pain scales[68-70]. In a systematic review of the psychometric properties, interpretability and feasibility of self-report pain

intensity measures for use in clinical trials in children and adolescents, the Wong Baker FACES, is reported to have reliability, validity, high feasibility, and responsivity in terms of detecting change in children's pain intensity for ages 3 to18 years[67].

2.2 Rationale

An extensive literature review is presented in section 2.1, in support of the clinical relevance of gabapentin, particularly in the setting of acute nociceptive pain.

Our hypothesis is that the addition of gabapentin to the current standard regimen of non-steroidal anti-inflammatory drugs and opioids, in the ACS of VOC-related pain, will improve the quality of pain control. The rationale supporting this expected effect includes the following:

a. The concept of "rational poly-pharmacy", which supports the concurrent use of drugs with distinctly different mechanisms of action to produce analgesia [30, 71]. Gabapentin-related analgesia is based on a different mechanism of action (at the α-2-δ subunit of the voltage-dependent calcium channel) than opioid analgesia (mu opioid receptor agonist effect) and non-steroidal anti-inflammatory drugs (cyclooxygenase inhibition);

b. Proven analgesic efficacy in the acute pain setting of postoperative pain in adults [13, 14] and children [11]. Additional evidence is provided in the literature review section of the background, based on 43 references.

c. Evidence that one of the mechanisms of acute pain in the VOC may be a neuropathic mechanism, based on demonstration of hyperalgesia and allodynia in animal models of sickle cell disease [72, 73]; hyperalgesia and allodynia are clinical characteristics of neuropathic pain;

d. Evidence that the combination of opioid and gabapentin is more effective than either one intervention alone, in the context of chronic pain [30];

Repetitive VOC events and associated acute pain episodes, like any other repetitive pain events, may contribute to the development of neuroplasticity and central sensitization. The neuronal phenomena of neuroplasticity and central sensitization are responsive to therapy with gabapentin [74-78]. Furthermore, there is evidence from animal studies that gabapentin is more effective in modulating nociceptive transmission in the presence of inflammation [74] and central sensitization [75], and the potency of the

antinociceptive effect is directly related to the intensity of sensitization [76]. The presence of both phenomena of inflammation and neuropathic pain mechanisms has been supported by the finding of neurochemical changes in the spinal cord and peripheral nerves in the transgenic sickle mouse model [73], and pain has been found to be related to a mechanism of ischemia and reperfusion injury, which exacerbates hyperalgesia [72]. Based on the contribution of neuroplasticity and central sensitization in the development of pain in repetitive VOC episodes [12] and the evidence of efficacy of gabapentin in modulating nociceptive mechanisms associated with inflammation and central sensitization, we expect an intervention with gabapentin for VOC pain to provide analgesic efficacy.

3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

According to institutional and NIH policy, the study will recruit research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

3.1 Inclusion Criteria

3.1.1 Participant must have sickle cell disease (any genotype), documented in the St. Jude medical record.
3.1.2 Participant must be seeking care for acute vaso-occlusive pain at St. Jude Children's Research Hospital.
3.1.3 Participant age must be ≥1 year and <21 years.

3.2 Exclusion Criteria

3.2.1 Prior randomization in this study.
3.2.2 Mild pain (score <4), or pain for which treatment with opioid is not indicated.
3.2.2 Pregnant or lactating females.
3.2.3 Decreased GFR (<60ml/min/1.73m^2) as estimated by the revised Schwartz equation.
3.2.4 Current treatment with gabapentinoid drugs (gabapentin or pregabalin).
3.2.5 Known seizure disorder.
3.2.6 Current treatment with antiepileptic agents.

3.2.5 Pain in combination with other clinical symptoms that require additional interventions, including fever with focus, acute chest syndrome, acute injury, or splenic sequestration.
3.2.6 Allergy to gabapentin.
3.2.7 Current participation in another research study with an IND/IDE agent (including SCATE and TWiTCH trials).
3.2.8 Inability or unwillingness of research participant or legal guardian/representative to give written informed consent.

3.3 Research Participant Recruitment and Screening

St. Jude patients with sickle cell disease will be educated about the availability of this study by study staff or hematology staff as appropriate during routine visits to the clinic. Informational flyers will be available for distribution (Appendix III). Providing information to patients and family in advance of an acute pain crisis should assist in the informed consent process by giving patients the opportunity to ask questions and consider options prior to a qualifying pain event.

Potentially eligible patients will be referred to the study team from the primary clinical team (Hematology Service) when the patient calls or arrives at the acute care setting with complaint of vaso-occlusive pain crisis. With the agreement of the primary clinical team, a study team member will approach the patient to initiate/continue informed consent discussions while standard pain management workup is ongoing.

When informed consent is obtained and the patient is enrolled, a member of the study team will inform the pharmacy and the randomization procedure will be initiated. The pharmacy order sets will be activated for the study drug. Delegated clinicians will order the study drug as per protocol section 4.0.

3.4 Enrollment on Study at St. Jude

A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, and will complete and sign the 'Participant Eligibility Checklist'. The study team will enter the eligibility checklist information into the Patient Protocol Manager (PPM) system. Eligibility will be reviewed, and a research participant-specific consent form and assent document (where applicable) will be generated. The complete signed

consent/assent form(s) must be faxed or emailed to the CPDMO at [redacted] to complete the enrollment process.

The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member is on call Saturday, Sunday, and holidays from 8:00 am to 5:00 pm. Enrollments may be requested during weekends or holidays by calling the CPDMO "On Call" cell phone [redacted] or referencing the "On Call Schedule" on the intranet).

3.5 Procedures for Identifying and Randomizing Research Participants

Eligibility of research participants will be confirmed between the study staff and treating clinician from the Hematology service. A member of the study team will then approach the patient and the legally authorized representative regarding the study. If the research participant and/or parent agree to participate, the randomization plan established by the study biostatistician will be accessed according to Section 11.2.

4.0 TREATMENT PLAN

4.1 Treatment

Upon each participant's enrollment, study staff will randomize the participant to one of 2 possible treatment arms (see section 11 for randomization procedure) and order the study treatment. The pharmacy will dispense the dose of study treatment (gabapentin vs. placebo) to the clinic or medicine room as soon as possible.

Study drug and other interventions will be administered and documented according to hospital policy by any appropriate clinical staff. All caregivers and study personnel will be blinded to the treatment assignment. Based on previous research experience at St. Jude, administration of the study drug is estimated to occur no later than 2 hours after patient's first opioid pain medication in the acute care setting.

4.2 Dose Modifications

Medication dosing may be modified for research recipients based upon actual body weight or adjusted ideal body weight when clinically indicated. Criteria

for medication calculations based on body weight/body surface area can be found in any version of the St. Jude Formulary. Medication doses may be rounded to the nearest integer or to the nearest appropriate quantity when clinically or pharmaceutically indicated as per the MD and PharmD.

The maximum dose is 900mg.

4.3 Concomitant Therapy

It is expected that participants in this study may be receiving concomitant therapies unrelated to the primary interests of this study. Only the study treatment and IV administered pain control treatments will be analyzed to determine the study outcomes. Patients on long-term treatments for sickle cell disease (e.g. hydroxyurea or chronic transfusion therapy) will be recorded for analysis.

4.4 Supportive Care

Primary pain management for the participant is of consummate importance. Investigators expect for participants to receive standard pain management, which could include IV fluids, opioid pain medicine, NSAIDS, and/or other interventions. Participants may show additional clinical signs warranting evaluation, such as fever or hypoxia, and will be evaluated appropriately.

Orders for standard pain management or other clinical interventions may be performed concurrently with administration of study drug. Caregivers are encouraged to refer to hospital policy for assessing, documenting, and reporting pain and other symptoms to the clinical team. Comprehensive sickle cell care will be managed by the Hematology team.

5.0 DRUG/DEVICE/BIOLOGIC AGENT INFORMATION

To allow for the study team and participants to remain blinded to the treatment assignment, the study drug will be labeled by the pharmacy as Gabapentin/Placebo (PMVOC 100 mg/mL) followed by applicable dose and administration instructions.

5.1 GABAPENTIN (Neurontin®)

Source and Pharmacology: Gabapentin is a white to off-white crystalline solid that is freely soluble in water. Its mechanism of action in preventing

seizures is not known. Gabapentin is not appreciably metabolized in humans; pharmacological effects are from the activity of the parent compound. It is eliminated unchanged in the urine. Patients with renal impairment should have dosage adjustments. Administration with food has little effect on absorption of gabapentin. In a single-dose gabapentin pharmacokinetics study in healthy infants and children, the mean maximum concentration was achieved 2.31 hours after a single oral dose in 48 children ages 1 month to 12 years of age. Dosing for 1 month to 2 years of age of the immediate-release gabapentin syrup was 10 mg/kg. Dosing for children greater than 2 years of age of the immediate-release capsules was based on weight and ranged from 8 mg/kg to 12.5 mg/kg as follows: 200 mg for 16 to 25 kg; 300 mg for 26 to 36 kg; 400 mg for 37 to 50 kg. The mean maximum concentrations were 3.74 mcg/mL for < 5 years of age (n=27) and 4.52 mcg/mL for ≥ 5 years of age (n=21). The single dose of gabapentin was well tolerated with seven participants reporting mild treatment-associated adverse events. The adverse events included asthenia, truncal ataxia, dizziness, drowsiness, somnolence, and vomiting [79].

Formulation and Stability: Gabapentin is supplied as an oral suspension containing 100 mg/mL. The St. Jude Children's Research Hospital Pharmacy will compound an oral suspension from commercially available capsules following pediatric drug formulation worksheets previously agreed upon by the FDA (Appendix IV). The oral suspension is stable for 3 months under refrigerated conditions between 2 and 8°C (36 and 46°F). The oral suspension will be stored between 2 and 8°C (36 and 46°F) in amber plastic prescription bottles for up to 3 months with continuous temperature monitoring.

Toxicity: Patients 3 – 12 years old treated with gabapentin for epilepsy reported the following central nervous system related adverse events: emotional lability, hostility, thought disorder and hyperkinesia in addition to CNS depression (dizziness, somnolence, fatigue, ataxia, and nystagmus). In placebo controlled trials of gabapentin in children taking other antiepileptic drugs, the following were also seen at higher frequency in the treatment group than the placebo group: viral infection, bronchitis, pharyngitis, rhinitis, respiratory infection, coughing, otitis media, fever, nausea and/or vomiting, diarrhea, depression, headache, diplopia, blurred vision, nervousness, seizures, pruritus, dyspepsia, constipation, weight gain, anorexia, leukopenia, back pain, and peripheral edema.

Do not administer within two hours of aluminum or magnesium containing antacids.

Supplier: Commercially available

Dosage and Route of Administration: Participants randomized to the active treatment arm will receive approximately 15 mg/kg gabapentin PO one time, as soon as feasible after enrollment. The maximum dose is 900mg (9mL).

5.2 PLACEBO

Patients randomized to the placebo arm will receive oral suspension similar in appearance, quantity and taste to the active treatment arm. Placebo suspension will be compounded with commercially available suspending and flavored syrup vehicles (Ora Plus/Ora Sweet) with flavoring added (Appendix V). The solution will be stored in the refrigerator. Placebo suspension will be prepared by the St. Jude Children's Research Hospital Pharmacy.

6.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

Subsections of 6.0 are in tabular form in Appendix I.

6.1 Pre-Study Evaluations

At a minimum, one baseline pain assessment will be documented in the medical record upon presentation to the acute care setting. Participants may have received opioids or other pain relieving interventions from home supply prior to arrival.

Prior to enrollment, glomerular filtration rate estimate will be calculated using the Schwartz equation based on the patient's most recent clinically obtained creatinine value documented in MILLI not more than 6 months prior to the pain event.

Female patients of childbearing potential must have documentation in MILLI of negative pregnancy test not more than 2 weeks prior to enrollment. Females currently receiving Depo-Provera at St. Jude may use documentation of negative pregnancy up to 6 weeks prior to enrollment. Female participants without negative test on record as described should have negative test documented in MILLI prior to enrollment. Either serum or urine testing may be used.

6.2 Evaluations During Therapy

Data for research purposes will be collected from the hospital medical records for the event, including visit duration, pain scores, and IV administered pain interventions given, as performed according to hospital standards of care. Only St. Jude pharmacists are unblinded to treatment assignment.

Pain assessments throughout the acute event will be performed by any clinical staff as per hospital standards (Appendix II). Researchers will analyze pain scores at baseline (at presentation), 15 minutes prior to or 15 minutes after the time of study drug administration, at 3 hours after study drug administration, and at point of decision for either admission or discharge to home (for patients who continue to be treated for pain longer than 3 hours after study drug is administered).

The pain scales used are the numerical rating system, the Faces Pain Scale, and the FLACC pain scale (for patients 7 years or older, ages 4-6 years, or less than 4 years, respectively) (Appendix II). Patients unwilling or unable to provide a score on the age-appropriate scale may use another scale if indicated.

Clinicians will obtain other studies as needed for good patient care.

6.3 Response Evaluations

No special tests and/or evaluations are required to evaluate response during study treatment. Significant pain will be treated by the primary care team as clinically indicated.

6.4 Off-Study Evaluations

Pain scores will be captured at 3 hours after the study drug is administered. The 3 hours post study drug pain score may be obtained up to 30 minutes before or after the 3 hour time point. The 3 hours post study drug pain score can be collected either in person or via phone. Patients who need additional pain management or other care will have a pain score at the time of decision for admission or discharge home.

Participants will be taken off study after a toxicity evaluation is performed / attempted within 72 hours following study drug administration (see section 7.2).

6.5 Long-Term Follow-up Evaluations

No long-term evaluations are planned.

Participants will be notified of their treatment assignment (gabapentin or placebo) after the completion of data collection for the last participant enrolled. Notification will be performed by a member of the study team in person (when feasible) or by letter at the earliest convenience of the study team and documented in the study files.

7.0 EVALUATION CRITERIA

7.1 Response Criteria

The response to therapy will be measured by pain intensity scores and total opioid use as described in the study objectives.

7.2 Toxicity Evaluation Criteria

Toxicity will graded according to the NCI CTCAE (version 4.0). Only new or worsening problems (i.e. significant changes in lab values from baseline) occurring after the administration of study drug will be captured for this study, as sickle cell patients may have steady-state or pre-existing values that fall in the range of toxicity per the CTCAE (e.g. anemia, fever, pain). Worsening pain scores after enrollment will not be captured or reported as AEs, but will be managed clinically. Hospital admission for VOC is an expected outcome and will not be captured/reported as an AE.

All participants must remain at St. Jude for at least 3 hours following administration of study drug to allow for monitoring of toxicity.

Participants that were discharged will be contacted by study staff between 24 and 72 hours following the administration of study drug to screen for unexpected events. Patients that were admitted after administration of the study drug will be monitored through hospital records to determine if any unexpected events occurred. These patients will also be contacted directly by study staff. Patients will remain on study until discharged so all clinical notes can be reviewed to determine toxicity.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF-STUDY CRITERIA

8.1 Off-therapy criteria

Because study therapy consists of a single oral dose of study drug, there are no off-therapy criteria. Refer to section 8.2, Off-Study Criteria.

8.2 Off-Study Criteria

8.1.1 Death
8.1.2 Lost to follow-up
8.1.3 Request of the Patient/Parent
8.1.4 Refusal of therapy
8.1.5 Discretion of the Study PI, such as the following
- The researcher decides that continuing in the study would be harmful
- A treatment is needed that is not allowed on this study
- The participant's condition gets worse
- New information is learned that a better treatment is available, or that the study is not in the participant's best interest

8.1.6 Study evaluations are complete
8.1.7 Unblinding of participant or study team to participant's treatment assignment

9.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

9.1 Reporting Adverse Experiences and Deaths

Principal investigators are responsible for promptly reporting to the IRB any adverse events that are unanticipated, serious, and that may represent potential harm or increased risk to research participants. When an unanticipated death occurs, the PI should report it to the Director of the Office of Human Subjects' Protection immediately, by phone: [redacted]

A reportable event entry into TRACKS should follow within 48 hours. Serious, unanticipated, and related or possibly related events must be reported within 10 working days. At the same time, the investigator will notify the study sponsor (NIH or pharmaceutical company), cooperative group, and/or the FDA, as appropriate. To report adverse events in gene therapy trials,

investigators should use specific RAC forms found at http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc .

The principal investigator is responsible for reviewing the aggregate toxicity reports and reporting to the IRB if the frequency or severity of serious toxicities exceed those expected as defined in the protocol or based on clinical experience or the published literature. Any proposed changes in the consent form or research procedures resulting from the report are to be prepared by the study team and submitted with the report to the IRB for approval.

The following definitions apply:

A serious event refers to any event in which the outcome is fatal or life-threatening, results in permanent disability, causes inpatient hospitalization or prolongs existing inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. Hospitalization due to the presenting VOC will not be reported as a serious event.

An unanticipated adverse event refers to those not identified in their nature, severity, or frequency in the current risk documents (e.g., investigator's brochure), or consistent with the investigational plan.

The following are considered reportable: Any injuries, serious event or other unanticipated adverse events involving risk to participants or others which occur at a frequency above that considered acceptable by the investigators and the IRB. (FDA) As described in HRPP Policy 01.720, the OHSP Director or designee performs the initial review of unanticipated problems or serious adverse event reports. Internal reports of events that are unanticipated, serious, and related or possibly related to study interventions or procedures are then forwarded to the IRB Chair or designee and if necessary, referred to the full IRB. Based on the frequency and seriousness of adverse events, the IRB Chair or Committee may deem it necessary to suspend or terminate a research study or studies.

9.2 Reporting to the Sponsor and/or Federal Agencies

9.2.1 Notification of Federal Agencies by Investigator

Copies of all correspondence to the St. Jude IRB, including serious adverse event reports, are provided to the St. Jude Office of Regulatory

Affairs via the electronic reporting system (TRACKS). All FDA related correspondence and reporting will be conducted through the Regulatory Affairs Office.

The FDA will be notified in writing (IND safety report) of any serious and unexpected adverse event associated with an investigational treatment or device. Annual reports, which will include the up-to-date clinical and safety data, will be submitted to the FDA at least annually.

9.2.2 Recording Adverse Events and Serious Adverse Events

Adverse events will be evaluated and documented by the clinical staff and investigators. The CRAs are responsible for documenting adverse events and entering them into the CRIS protocol-specific database. AEs that are classified as serious, unexpected, and at least possibly related will be reported expeditiously to the St. Jude IRB as described in protocol section 9.1. All other events will be reported to the IRB as part of the continuing review process.

As stated in section 7.2, only new or worsening problems occurring after the administration of study drug will be reported as adverse events, as sickle cell patients may have pre-existing conditions that fall in the range of toxicity per the CTCAE and are not related to study drug (e.g. anemia, fever, pain). Any event occurring more than 72 hours after administration of study drug will not be captured.

9.3 Emergency Unblinding

In the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product is essential for the clinical management or welfare of the subject, an investigator or other physician managing the subject may decide to unblind that subject's treatment code.

The physician managing the medical emergency or serious condition should attempt to contact the principal investigator to discuss options prior to unblinding, and the principal investigator should approve the unblinding, when applicable. However, ensuring patient safety is the primary objective when the decision to unblind the treatment assignment is made.

The principal investigator or designated study personnel will complete an order in MILLI with the request to unblind the patient's treatment arm. The principal

investigator or treating clinician will contact pharmacy to receive the unblinding information.

All occurrences of emergency unblinding will be reported to the IRB according to the criteria established in protocol section 9.0, and the FDA, when applicable. In a majority of cases, emergency unblinding will occur while managing a serious adverse event (SAE), and will therefore be reported with the SAE. If the unblinding event is not directly associated with an SAE, the same timeline and mechanism for reporting SAEs will be used to notify the IRB of the event (section 9.1).

10.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

10.1 Data Collection

Members of the clinical care team will complete documentation in the electronic medical record for each study encounter. Data will then be abstracted into a secure database by study staff, which serves as the electronic case report forms (eCRFs). Records from the study which identify the study participant will be kept confidential in a secured area.

10.2 Study Monitoring

Source document verification of eligibility for all SJCRH cases will be performed within two weeks of completion of enrollment. This will include verification of appropriate documentation of consent. Monitoring of timeliness of serious adverse event reporting will be done as events are reported in TRACKS.

Monitoring of this protocol is considered to be in the High Risk 3 category. The Monitoring Plan is outlined in a separate document from this protocol, but has been submitted for review and approval by the Clinical Trials Scientific Review Committee and the Institutional Review Board.

Continuing reviews by the IRB and CT-SRC will occur at least annually. In addition, SAE reports in TRACKS are reviewed in a timely manner by the IRB/ OHSP.

10.3 Confidentiality

Source documents from the study which identify the participant will be kept confidential in a secured area and a password-protected database. Any list containing the study number and the medical record number will be maintained in a password-protected electronic file and will be destroyed after all data have been analyzed.

The medical records of study participants may be reviewed by the St. Jude IRB, FDA, clinical research monitors, and other authorized regulatory personnel.

11.0 STATISTICAL CONSIDERATIONS

This is a double-blind placebo-controlled clinical trial evaluating the effect of gabapentin when added to standard pain management for patients with sickle cell disease experiencing acute pain crisis in the ambulatory care setting. The primary study objective is to assess the analgesic efficacy of gabapentin for pain during VOC in participants with SCD, by comparing the proportion of participants with a decrease of ≥ 33% in pain scores between presentation to the acute care setting and assessment at 3 hours post administration of study drug, in the gabapentin and placebo groups. The intention-to-treat principle will be followed and all eligible, randomized subjects will be analyzed in the primary analysis as randomized.

11.1 Sample size

Retrospective review of 26 months of records (August 1, 2010 to October 1, 2012) indicated that 137 patients, ages 1-18, experienced VOC due to SCD and were administered opioids. We analyzed the pain scores from a subset of 40 patients between the ages of 8 and 18 who had received opioid(s) and also had pain scores documented at baseline and end of the visit. We found a reduction in the pain scores from baseline to discharge or admission of ≥ 33% [81-83] in 45% of patients (18/40). The hypothesis is that treatment with gabapentin has better analgesic efficacy than placebo in the treatment of pain during VOC, when added to the current standard of care for pain during VOC which comprises opioids and non-steroidal anti-inflammatory drugs. An increase in the proportion of patients with ≥ 33% reduction of the pain scores from 45% to at least 65% between presentation and assessment at 3 hours post administration of study drug is considered clinically meaningful [81-83].

Let P_t and P_c be the proportions of participants with a decrease of ≥ 33% in pain scores between presentation to the acute care setting (ACS) and 3 hours post study drug administration, in the gabapentin and placebo groups,

respectively. We wish to test whether there is a significant difference in the proportions of participants with a decrease of ≥ 33% in pain scores in two groups and formulate the following hypothesis: the null hypothesis H_0: $\Delta = \underline{P_t} - \underline{P_c} = 0$ against the 1-sided alternative hypothesis H_1: $\Delta > 0$. With the design parameters of a type I error rate (α) of 0.05 and a type II error rate (β) of 0.2, assuming one interim analysis and $\Delta = 0.2$ under H_1, we will need a total of 166 patients (83 per group) for our two sample test. The interim analysis will be conducted to assess efficacy and futility, when there are 96 subjects randomized. We will recommend that the trial will be halted for efficacy (in favor of H_1) if the nominal p-value for the interim analysis is less than or equal to 0.0143. We will recommend the trial should be halted for futility (in favor of H_0) if the nominal p-value for the interim analysis is greater than or equal to 0.2249. If H_0 is true, this interim analysis has a 79% probability of stopping in favor of H_0. If H_1 is true, this interim analysis has a 53% probability of stopping in favor of H_1. To account for the planned interim analysis, the final analysis will be at the nominal p-value of 0.0447; thus maintaining the overall type I error rate at 0.05. This plan is based on the binomial two-sample difference in proportions with a non-binding interim analysis based on power family spending functions with alpha and beta spending parameters set to 0.1 (EAST software v5.3).

Accrual: Based on the retrospective data, we can expect to prospectively evaluate 63 patients for enrollment per year. If we enroll and randomize 2/3 of the eligible patients, the enrollment would reach 42 patients per year. Therefore, it will take approximately four years to enroll all 166 patients necessary to address the primary objective.

11.2 Randomization

Eligible patients with an established diagnosis of pain and VOC will be consented and randomized to receive a single dose of gabapentin or placebo. Morphine or other opioid and non-steroidal anti-inflammatory drugs will be available to both groups as needed for pain and will be administered according to the current standard of care for pain in VOC from the Department of Hematology. Randomization will be performed in SJCRH pharmacy by a pharmacist, using the randomization program developed by the Department of Biostatistics. The randomization will be stratified by three age categories (1-3yr, 4-6yr, ≥7yr) for which distinct pain assessment tools are applied and for 2 pain scores categories at assessment at presentation: 4- 6 and 7-10, respectively. A

block randomization with block sizes varying randomly between 4 and 6 will be used in each stratum.

11.3 Statistical analysis

11.3.1 Primary Objective

To assess the analgesic efficacy of gabapentin (vs. placebo) for pain during VOC in participants with SCD. A response to study drug will be defined by a decrease in pain score of ≥33% between presentation to the acute care setting and assessment at 3 hours post administration of study drug.

For each patient, if the reduction of the pain scores between presentation to the acute care setting and 3 hours post administration of study drug is 33% or greater, then this patient will be defined as having a successful intervention. The proportions of successful interventions in the gabapentin and placebo groups will be estimated and compared using Z-test (PROC FREQ procedure in SAS).

11.3.2 Secondary Objective

To compare the total morphine dose or morphine equivalent (mg/kg) used to control pain during VOC between presentation to the acute care setting and assessment at 3 hours post administration of study drug in the gabapentin vs. placebo groups.

Summary statistics of the total morphine dose or morphine equivalent (mg/kg) used to control pain during VOC between presentation to the acute care setting and 3 hours post administration of study drug, in the gabapentin and placebo groups will be provided. Test of normality such as Shapiro-Wilk test will be applied to the total morphine dose or morphine equivalent (mg/kg) to examine their deviation from the normal distribution. A two-sample t-test or Wilcoxon rank sum test will be used to compare the total morphine dose or morphine equivalent (mg/kg) for the gabapentin vs. placebo groups depending on whether the normality assumption of the data holds.

11.3.3 Exploratory Objectives

1. To assess the analgesic efficacy of gabapentin for pain during VOC in participants with SCD, as defined by a decrease in pain scores of ≥33%

between presentation to the acute care setting and the point of decision for either hospital admission or discharge to home, in the gabapentin and placebo groups.

Statistical methods used to analyze this objective will be the same as those used for the primary objective.

2. To compare the total morphine dose or morphine equivalent (mg/kg) used to control pain during VOC between presentation to the acute care setting and the point of decision for either admission or discharge to home, in the gabapentin and placebo groups.

   Statistical methods used to analyze this objective will be the same as those used for the secondary objective.

3. To compare the rate of admission related to pain management, in the gabapentin vs. placebo groups.

   Statistical methods used to analyze this objective will be the same as the analysis used for the primary objective.

4. To compare the change in pain score from time of administration of study drug to assessment at 3 hours post administration of study drug in the gabapentin vs. placebo groups.

   The numeric changes in pain scores will be compared using the statistical methods of the secondary objective. Changes in pain score will also be evaluated as a proportion of those with a decrease of ≥33% and analyzed by the methods of the primary objective.

5. To compare the change in pain score from time of administration of study drug to the point of decision for either admission or discharge to home, in the gabapentin and placebo groups.

   The numeric changes in pain scores will be compared using the statistical methods of the secondary objective. Changes in pain score will also be evaluated as a proportion of those with a decrease of ≥33% and analyzed by the methods of the primary objective.

12.0 OBTAINING INFORMED CONSENT

Eligible patients will be approached by a member of the study team regarding the study purpose, methods and design details. Both verbal and written assent and consent procedures will be completed in a private room and follow our institutional guidelines.

Because acute VOC pain and timely treatments can interfere with adequate participation in the consent discussion, the study team has requested modifications to the informed consent process. Potentially eligible participants who are age 18 or older may ask to select a surrogate decision maker for the consent process. In this case, investigators will follow the St. Jude HRPP policy 01.725, "Surrogate Consent for Human Subjects Research". Likewise, potential participants who are less than 18 years old may decline to give written or verbal assent for participation; the written consent will be completed by the patient's legally authorized representative acting on behalf of the interests of the minor participant.

The consent/assent process will be documented in the medical record per institutional guidelines. Research participants and parents may decline participation without repercussions. Refusals will be documented in the research records and examined for any possible patterns. All research participants who meet eligibility criteria regardless of gender or minority status are fully eligible to participate in this study. All data will be kept confidential and stored in a locked file inside locked offices.

12.1 Consent at Age of Majority

The age of majority in the state of Tennessee is 18 years old. Because study drug is given only once, reconsenting at the age of majority is not expected.

12.2 Consent When English is Not the Primary Language

When English is not the patient, parent, or legally authorized representative's primary language, the Social Work department will determine the need for an interpreter. This information documented in the participant's medical record. Either a certified interpreter or the telephone interpreter's service will be used to translate the consent information. The process for obtaining an interpreter and for the appropriate use of an interpreter is outlined on the Interpreter Services, OHSP, and CPDMO websites.

13.0 REFERENCES

1. Backonja, M., A. Beydoun, et al., *Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial.* JAMA, 1998. **280**(21): 1831-6.
2. Rowbotham, M., N. Harden, et al., *Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial.* JAMA, 1998. **280**(21): 1837-42.
3. van de Vusse, A.C., S.G. Stomp-van den Berg, et al., *Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1 [ISRCTN84121379]*. BMC Neurol, 2004. **4**: 13.
4. Ho, K.Y., T.J. Gan, and A.S. Habib, *Gabapentin and postoperative pain--a systematic review of randomized controlled trials.* Pain, 2006. **126**(1-3): 91-101.
5. Fink, K., D.J. Dooley, et al., *Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex.* Neuropharmacology, 2002. **42**(2): 229-36.
6. Taylor, C.P., *The biology and pharmacology of calcium channel alpha2-delta proteins Pfizer Satellite Symposium to the 2003 Society for Neuroscience Meeting. Sheraton New Orleans Hotel, New Orleans, LA November 10, 2003.* CNS Drug Rev, 2004. **10**(2): 183-8.
7. Field, M.J., R.J. Oles, et al., *Gabapentin (neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents.* Br J Pharmacol, 1997. **121**(8): 1513-22.
8. Feng, Y., M. Cui, and W.D. Willis, *[Effect of anticonvulsant gabapentin on visceral nociception and its relationship with amino acid neurotransmitters released from spinal cord]*. Beijing Da Xue Xue Bao, 2003. **35**(3): 307-10.
9. Matthews, E.A. and A.H. Dickenson, *A combination of gabapentin and morphine mediates enhanced inhibitory effects on dorsal horn neuronal responses in a rat model of neuropathy.* Anesthesiology, 2002. **96**(3): 633-40.
10. Gilron, I., J. Biederman, et al., *Gabapentin blocks and reverses antinociceptive morphine tolerance in the rat paw-pressure and tail-flick tests.* Anesthesiology, 2003. **98**(5): 1288-92.
11. Rusy, L.M., K.R. Hainsworth, et al., *Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial.* Anesth Analg, 2010. **110**(5): 1393-8.
12. Ballas, S.K., K. Gupta, and P. Adams-Graves, *Sickle cell pain: a critical reappraisal.* Blood, 2012.
13. Menigaux, C., F. Adam, et al., *Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery.* Anesth Analg, 2005. **100**(5): 1394-9, table of contents.
14. Fassoulaki, A., K. Patris, et al., *The analgesic effect of gabapentin and mexiletine after breast surgery for cancer.* Anesth Analg, 2002. **95**(4): 985-91, table of contents.
15. Straube, S., S. Derry, et al., *Single dose oral gabapentin for established acute postoperative pain in adults.* Cochrane Database Syst Rev, 2010(5): CD008183.
16. Seib, R.K. and J.E. Paul, *Preoperative gabapentin for postoperative analgesia: a meta-analysis.* Can J Anaesth, 2006. **53**(5): 461-9.

17. Hurley, R.W., S.P. Cohen, et al., *The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis.* Reg Anesth Pain Med, 2006. **31**(3): 237-47.
18. Peng, P.W., D.N. Wijeysundera, and C.C. Li, *Use of gabapentin for perioperative pain control -- a meta-analysis.* Pain Res Manag, 2007. **12**(2): 85-92.
19. Dirks, J., B.B. Fredensborg, et al., *A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy.* Anesthesiology, 2002. **97**(3): 560-4.
20. Pandey, C.K., S. Priye, et al., *Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy.* Can J Anaesth, 2004. **51**(4): 358-63.
21. Pandey, C.K., S. Sahay, et al., *Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy.* Can J Anaesth, 2004. **51**(10): 986-9.
22. Pandey, C.K., D.V. Navkar, et al., *Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study.* J Neurosurg Anesthesiol, 2005. **17**(2): 65-8.
23. Pandey, C.K., V. Singhal, et al., *Gabapentin provides effective postoperative analgesia whether administered pre-emptively or post-incision.* Can J Anaesth, 2005. **52**(8): 827-31.
24. Turan, A., B. Karamanlioglu, et al., *Analgesic effects of gabapentin after spinal surgery.* Anesthesiology, 2004. **100**(4): 935-8.
25. Turan, A., B. Karamanlioglu, et al., *The analgesic effects of gabapentin after total abdominal hysterectomy.* Anesth Analg, 2004. **98**(5): 1370-3.
26. Turan, A., D. Memis, et al., *The analgesic effects of gabapentin in monitored anesthesia care for ear-nose-throat surgery.* Anesth Analg, 2004. **99**(2): 375-8.
27. Tuncer, S., H. Bariskaner, et al., *Effect of gabapentin on postoperative pain: A randomized, placebo-controlled clinical study.* Pain Clinic, 2005. **17**(1): 95-99.
28. Radhakrishnan, M., P.K. Bithal, and A. Chaturvedi, *Effect of preemptive gabapentin on postoperative pain relief and morphine consumption following lumbar laminectomy and discectomy: a randomized, double-blinded, placebo-controlled study.* J Neurosurg Anesthesiol, 2005. **17**(3): 125-8.
29. Dierking, G., T.H. Duedahl, et al., *Effects of gabapentin on postoperative morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind trial.* Acta Anaesthesiol Scand, 2004. **48**(3): 322-7.
30. Gilron, I., J.M. Bailey, et al., *Morphine, gabapentin, or their combination for neuropathic pain.* N Engl J Med, 2005. **352**(13): 1324-34.
31. Turan, A., G. Kaya, et al., *Effect of oral gabapentin on postoperative epidural analgesia.* Br J Anaesth, 2006. **96**(2): 242-6.
32. Rorarius, M.G., S. Mennander, et al., *Gabapentin for the prevention of postoperative pain after vaginal hysterectomy.* Pain, 2004. **110**(1-2): 175-81.
33. Yoon, K., C. Kim, et al., *Analgesic effects of gabapentin on post-hysterectomy pain.* Korean J Anesthesiol, 2001. **41**(6): S13-S18.
34. Turan, A., P.F. White, et al., *Gabapentin: an alternative to the cyclooxygenase-2 inhibitors for perioperative pain management.* Anesth Analg, 2006. **102**(1): 175-81.
35. Clarke, H., R.P. Bonin, et al., *The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis.* Anesth Analg, 2012. **115**(2): 428-42.

36. Kinney, M.A., C.B. Mantilla, et al., *Preoperative gabapentin for acute post-thoracotomy analgesia: a randomized, double-blinded, active placebo-controlled study.* Pain Pract, 2012. **12**(3): 175-83.
37. Clarke, H., K.R. Kirkham, et al., *Gabapentin reduces preoperative anxiety and pain catastrophizing in highly anxious patients prior to major surgery: a blinded randomized placebo-controlled trial.* Can J Anaesth, 2013.
38. Lee, J.H., H.K. Lee, et al., *The prophylactic effects of gabapentin on postoperative sore throat after thyroid surgery.* Korean J Anesthesiol, 2013. **64**(2): 138-42.
39. Short, J., K. Downey, et al., *A single preoperative dose of gabapentin does not improve postcesarean delivery pain management: a randomized, double-blind, placebo-controlled dose-finding trial.* Anesth Analg, 2012. **115**(6): 1336-42.
40. Adam, F., L. Bordenave, et al., *Effects of a single 1200-mg preoperative dose of gabapentin on anxiety and memory.* Ann Fr Anesth Reanim, 2012. **31**(10): e223-7.
41. Ajori, L., L. Nazari, et al., *Effects of gabapentin on postoperative pain, nausea and vomiting after abdominal hysterectomy: a double blind randomized clinical trial.* Arch Gynecol Obstet, 2012. **285**(3): 677-82.
42. Behdad, S., V. Ayatollahi, et al., *Effect of gabapentin on postoperative pain and operation complications: a randomized placebo controlled trial.* West Indian Med J, 2012. **61**(2): 128-33.
43. Deniz, M.N., N. Sertoz, et al., *Effects of preoperative gabapentin on postoperative pain after radical retropubic prostatectomy.* J Int Med Res, 2012. **40**(6): 2362-9.
44. Ozgencil, E., S. Yalcin, et al., *Perioperative administration of gabapentin 1,200 mg day-1 and pregabalin 300 mg day-1 for pain following lumbar laminectomy and discectomy: a randomised, double-blinded, placebo-controlled study.* Singapore Med J, 2011. **52**(12): 883-9.
45. Panah Khahi, M., A.A. Yaghooti, et al., *Effect of pre-emptive gabapentin on postoperative pain following lower extremity orthopaedic surgery under spinal anaesthesia.* Singapore Med J, 2011. **52**(12): 879-82.
46. Ucak, A., B. Onan, et al., *The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery.* J Cardiothorac Vasc Anesth, 2011. **25**(5): 824-9.
47. Spence, D., J. Goff, et al., *Perioperative administration of gabapentin for shoulder arthroscopy: a prospective, randomized, double-blind, placebo-controlled study.* AANA J, 2011. **79**(4 Suppl): S43-50.
48. Ghai, A., M. Gupta, et al., *A randomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy.* Saudi J Anaesth, 2011. **5**(3): 252-7.
49. Khan, Z.H., M. Rahimi, et al., *Optimal dose of pre-incision/post-incision gabapentin for pain relief following lumbar laminectomy: a randomized study.* Acta Anaesthesiol Scand, 2011. **55**(3): 306-12.
50. Moore, R.A., P.J. Wiffen, et al., *Gabapentin for chronic neuropathic pain and fibromyalgia in adults.* Cochrane Database Syst Rev, 2011(3): CD007938.
51. Syal, K., M. Goma, et al., *"Protective premedication": a comparative study of acetaminophen, gabapentin and combination of acetaminophen with gabapentin for post-operative analgesia.* J Anaesthesiol Clin Pharmacol, 2010. **26**(4): 531-6.

52. Bang, S.R., S.K. Yu, and T.H. Kim, *Can gabapentin help reduce postoperative pain in arthroscopic rotator cuff repair? A prospective, randomized, double-blind study.* Arthroscopy, 2010. **26**(9 Suppl): S106-11.
53. Amr, Y.M. and A.A. Yousef, *Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain.* Clin J Pain, 2010. **26**(5): 381-5.
54. Rapchuk, I.L., L. O'Connell, et al., *Effect of gabapentin on pain after cardiac surgery: a randomised, double-blind, placebo-controlled trial.* Anaesth Intensive Care, 2010. **38**(3): 445-51.
55. Molokie, R.E., Z.J. Wang, and D.J. Wilkie, *Presence of neuropathic pain as an underlying mechanism for pain associated with cold weather in patients with sickle cell disease.* Med Hypotheses, 2011. **77**(4): 491-3.
56. Wilkie, D.J., R. Molokie, et al., *Patient-reported outcomes: descriptors of nociceptive and neuropathic pain and barriers to effective pain management in adult outpatients with sickle cell disease.* J Natl Med Assoc, 2010. **102**(1): 18-27.
57. Brandow, A., R. Farley, and J. Panepinto. *Existence of Neuropathic Pain in Patients with Sickle Cell Disease*. in *54th ASH Annual Meeting*. 2012.
58. Merkel, S.I., T. Voepel-Lewis, et al., *The FLACC: A behavioral scale for scoring postoperative pain in young children.* Pediatr Nurs, 1997. **23**(3): 293-297.
59. Hockenberry, M. and D. Wilson, *Wong's Essentials of Pediatric Nursing*. 8th ed2009, St. Louis: Mosby.
60. Wong, D.L. and C.M. Baker, *Pain in children: comparison of assessment scales.* Pediatr Nurs, 1988. **14**(1): 9-17.
61. von Baeyer, C.L., *Children's self-reports of pain intensity: scale selection, limitations and interpretation.* Pain Res Manag, 2006. **11**(3): 157-162.
62. von Baeyer, C.L., L.J. Spagrud, et al., *Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity.* Pain, 2009. **143**(3): 223-7.
63. Manworren, R.C. and L.S. Hynan, *Clinical validation of FLACC: Preverbal patient pain scale.* Pediatr Nurs, 2003. **29**(2): 140-6.
64. McGrath, P.J., G.A. Walco, et al., *Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations.* J Pain, 2008. **9**(9): 771-83.
65. Voepel-Lewis, T., J. Zanotti, et al., *Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients.* Am J Crit Care, 2010. **19**(1): 55-61.
66. Tomlinson, D., C.L. von Baeyer, et al., *A systematic review of faces scales for the self-report of pain intensity in children.* Pediatrics, 2010. **126**(5): e1168-98.
67. Stinson, J.N., T. Kavanagh, et al., *Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents.* Pain, 2006. **125**(1-2): 143-57.
68. Chambers, C.T., K. Giesbrecht, et al., *A comparison of faces scales for the measurement of pediatric pain: children's and parents' ratings.* Pain, 1999. **83**(1): 25-35.
69. Chambers, C.T., J. Hardial, et al., *Faces scales for the measurement of postoperative pain intensity in children following minor surgery.* Clin J Pain, 2005. **21**(3): 277-85.

70. Luffy, R. and S.K. Grove, *Examining the validity, reliability, and preference of three pediatric pain measurement tools in African-American children.* Pediatr Nurs, 2003. **29**(1): 54-9.
71. Chaparro, L.E., P.J. Wiffen, et al., *Combination pharmacotherapy for the treatment of neuropathic pain in adults.* Cochrane Database Syst Rev, 2012. **7**: CD008943.
72. Cain, D.M., D. Vang, et al., *Mouse models for studying pain in sickle disease: effects of strain, age, and acuteness.* Br J Haematol, 2012. **156**(4): 535-44.
73. Kohli, D.R., Y. Li, et al., *Pain-related behaviors and neurochemical alterations in mice expressing sickle hemoglobin: modulation by cannabinoids.* Blood, 2010. **116**(3): 456-65.
74. Stanfa, L.C., L. Singh, et al., *Gabapentin, ineffective in normal rats, markedly reduces C-fibre evoked responses after inflammation.* Neuroreport, 1997. **8**(3): 587-90.
75. Iannetti, G.D., L. Zambreanu, et al., *Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans.* Proc Natl Acad Sci U S A, 2005. **102**(50): 18195-200.
76. Curros-Criado, M.M. and J.F. Herrero, *The antinociceptive effect of systemic gabapentin is related to the type of sensitization-induced hyperalgesia.* J Neuroinflammation, 2007. **4**: 15.
77. Gottrup, H., G. Juhl, et al., *Chronic oral gabapentin reduces elements of central sensitization in human experimental hyperalgesia.* Anesthesiology, 2004. **101**(6): 1400-8.
78. Tuchman, M., J.A. Barrett, et al., *Central sensitization and Ca(V)alpha(2)delta ligands in chronic pain syndromes: pathologic processes and pharmacologic effect.* J Pain, 2010. **11**(12): 1241-9.
79. Haig, G.M., H.N. Bockbrader, et al., *Single-dose gabapentin pharmacokinetics and safety in healthy infants and children.* J Clin Pharmacol, 2001. **41**(5): 507-14.
80. Nahata, M.C., *Development of two stable oral suspensions for gabapentin.* Pediatr Neurol, 1999. **20**(3): 195-7.
81. Farrar, J.T., *What is clinically meaningful: outcome measures in pain clinical trials.* Clin J Pain, 2000. **16**(2 Suppl): S106-12.
82. Farrar, J.T., J.A. Berlin, and B.L. Strom, *Clinically important changes in acute pain outcome measures: a validation study.* J Pain Symptom Manage, 2003. **25**(5): 406-11.
83. Farrar, J.T., R.K. Portenoy, et al., *Defining the clinically important difference in pain outcome measures.* Pain, 2000. **88**(3): 287-94.

APPENDICES

APPENDIX I: Schedule of Evaluations (**required)**

Event	Screen[1]	Entry	On Treatment			24-72 hours after study drug
			Acute care setting	3 hours after study drug	Decision to discharge from acute care or admit	
Informed Consent	X					
Pregnancy test	PRN					
Pain assessment	X	X[3]	PRN	X	X[2]	
Study drug		X				
Pain intervention	PRN	PRN	PRN	PRN		
Adverse event screen				X	X	X
Off study						X

[1]Routine pain interventions may begin before study entry/administration of study drug
[2]Patients who leave the ACU at the 3 hour time point will not have a fourth pain assessment captured
[3]Pain score will be recorded within 30 minutes of drug administration.

APPENDIX II:

TESTS PERFORMED FOR GOOD CLINICAL CARE

Guidelines for pain management at St. Jude are available in the hospital Policy and Procedure Manual accessible via the hospital intranet or paper-based copies in clinical areas.

Section VIII: Pain Management
- 8003 Guidelines for Pharmacologic Pain Management
- 8005 Nonpharmacologic Pain Management
- 8008 Standards of Care: Pain Management

Appendix III: Recruitment Materials

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Sickle Cell Research:
Pain Crisis Study

St. Jude doctors want to know if a medicine that is helpful for some cancer pain and surgery pain could also help sickle cell pain in young patients.

Who: Any St. Jude patient with sickle cell disease and a new pain crisis, between 1-21 years old

Where: The study takes place only at St. Jude, in the clinic or medicine room during a pain crisis.

How: When you arrive for your pain appointment, you may be asked if you would like to participate. A parent or legal guardian must be here to sign consent to participate.

What: Eligible patients will receive study drug by mouth **IN ADDITION TO** the standard pain medicines. The rest of the pain crisis visit is the same as usual. You will be asked for a pain score 3 hours after taking the study drug, either in person or by phone. Also, you will receive $25 for your participation.

Want to know more? Ask your sickle cell team for more information at any time. You may also call [redacted] during business hours to talk to the study team for details about the study.

Research Team: Dr. Anghelescu, Dr. Hankins, Dr. Wang, Olivia McGregor

Appendix IV: Gabapentin Drug Formulation

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

114 - ___/___/___-__
Batch Control Number

Pediatric Drug Formulation

Gabapentin (for PMVOC)	oral solution	100mg/mL	120mL
(Generic Name)	(Dosage Form)	(Concentration)	(Final Quantity)

Stability: 91 days ***Stability Reference:*** Pedia Neuro, 1999

Label:

Store: Refrigerated 2-8 C

Ingredient		Amt. Required	Amt. Used	Manufacturer / Lot #
Gabapentin capsule	300mg	40		
Ora-Plus and Ora-Sweet		50mL of each		
Anise Oil	3gtt/5mL	3.6mL		
Peppermint Oil	2gtt/5mL	2.4mL		

Directions:

Measure and add the 50mL of each Ora-Plus and Ora-Sweet to a prescription bottle. Empty the contents of all of the Gabapentin capsules into the bottle. Cover and shake the contents until the drug is evenly dispersed. Then add the appropriate measurements of the Anise oil and Peppermint oil. Cover again and shake to mix all ingredents well. Transfer the drug to a graduated cylinder to determine the remaining volume needed to qs to 120mL. Return to prescription bottle. Rinse the cylinder with the predetermined 1:1 Ora-Plus and Ora-Sweet. Add to bottle and shake. Label the bottle appropriately.

For Investigational Use Only

PLACE LABEL HERE

Created: 03/24/00
Updated:

Prepared By: _____ Checked By: _____

Appendix V: Gabapentin Placebo Drug Formulation

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

115-___/___/___-__
Batch Control Number

Pediatric Drug Formulation

Gabapentin Placebo (for PMVOC (Generic Name)	**Oral Solution** (Dosage Form)	(Concentration)	**60 mL** (Final Quantity)

Stability: 14 days ***Stability Reference:*** USP 795, pg 34

Label:

Store: Refrigerate 2-8 C

Ingredient		Amt. Required	Amt. Used	Manufacturer / Lot #
Microcrystalline Cellulose placebo caps size 0	1cap/10mL	6 caps		
Ora-Plus and Ora-Sweet		29.1 mL of each		
Anise Oil	1gtt/5mL	0.6 mL		
Peppermint Oil	2gtt/5mL	1.2 mL		

Directions:

Measure and add the Ora-Plus and Ora-Sweet to a prescription bottle. Empty the contents of each placebo capsule into the bottle. Cover and shake well until the ingredents are well dispersed. Add the Anise and Peppermint oils and shake well to mix all ingredents.

PLACE LABEL HERE

Created: 03/24/00
Updated:

Prepared By: _____ Checked By: _____