CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Fred Senatore MD, PhD, FACC
Review Completion Date	05 May 2015
Established Name	Aspirin, controlled release
(Proposed) Trade Name	DURLAZA
Therapeutic Class	Nonsteroidal anti-inflammatory drug
Applicant	New Haven Pharmaceuticals
Formulation(s)	Encapsulated Aspirin
Dosing Regimen	162.5 mg
Indication(s)	Secondary prevention of acute cardiovascular events
Intended Population(s)	Adults post cardiovascular events

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List of Abbreviations

ASA	Aspirin: acetyl salicylic acid
COX-1	Cyclooxygenase-1
CSR	Case Study Report
CV	Cardiovascular
DILI	Drug Induced Liver Disease
EC	Enteric-Coated
ID_{50}	Dose producing 50% of maximum inhibition
IPA	Inhibition of Platelet Aggregation
IR-ASA	Immediate Release Aspirin
IRB	Institutional Review Board
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intention to Treat
LD_{50}	Dose causing 50% mortality
MABEL	Minimum Anticipated Biological Effect Level
NOAEL	No Adverse Effect Level
NSAID	Nonsteroidal anti-inflammatory drug
OCP	Office of Clinical Pharmacology
PD	Pharmacodynamic
PG12	Prostacyclin
PK	Pharmacokinetics
SA	Salicylic Acid
SAE	Serious Adverse Events
SDR	Sprague-Dawley Rats
SOC	System Organ Class
TIA	Transient Ischemic Attack
TxA2, TxB2	Thromboxane (TxB2 is a degradation product of TxA2)
ULN	Upper Limit of Normal
WHO	World Health Organization

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1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of NHP-554C (DURLAZA®) for the indications listed in the aspirin monograph. The basis of this recommendation is:

- There is pharmacodynamic equivalence between DURLAZA® and immediate-release aspirin regarding inhibition of thromboxane synthesis and inhibition of platelet aggregation, as determined by the Office of Pharmacology.
- No empirical pharmacodynamic effect on prostacyclin suggesting a safety signal, based on legacy studies.
- No safety signals relative to immediate release aspirin.

1.2 Risk Benefit Assessment

This NDA did not present efficacy data. Therefore, a traditional efficacy / safety analysis was not performed. The risk/benefit assessment consequently focused on the relative safety of each aspirin formulation. Adverse events, serious adverse events, deaths, and gastrointestinal adverse events for both NHP-554C and immediate-release aspirin were compiled from the journal publications and the Applicant's study NHP-ASP-01 serving as the basis of approval. The results, shown on ***Table 14***, showed that the adverse event rate, serious adverse event rate and gastrointestinal adverse event rate were numerically lower for the NHP-554C groups compared to the immediate-release aspirin groups. The mortality rate for both the NHP-554C and immediate-release aspirin arms were identical. Therefore, no safety signals were detected for the Applicant's product relative to the immediate release formulation.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post-market risk evaluation or mitigation strategies are required.

1.4 Recommendations for Postmarket Requirements and Commitments

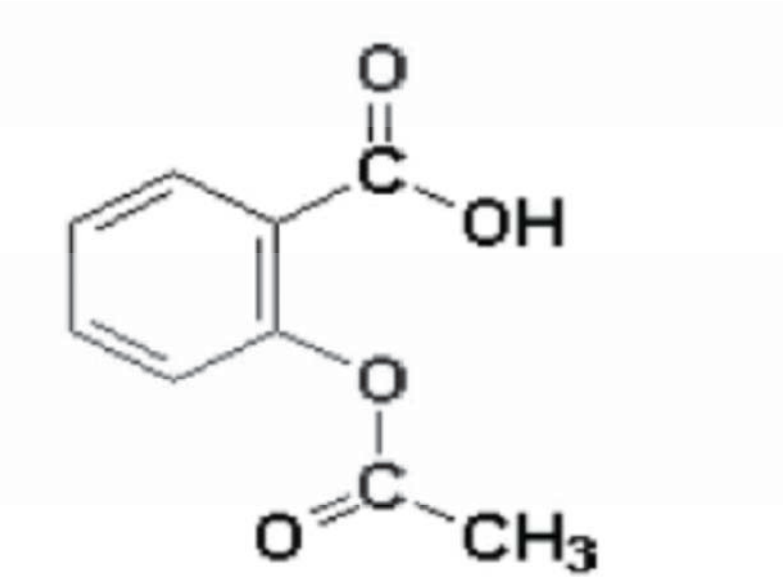
No post-market requirements and commitments are necessary.

2 Introduction and Regulatory Background

2.1 Product Information

NHP-554C is an encapsulated aspirin that is included within the nonsteroidal anti-inflammatory drug (NSAID) pharmacologic classification. NHP-554C is also referred to as Flamasacard®, Caspac®, Asacard®, Asacard XL®, Asacard LP®, and Therasacard®. The active ingredient in NHP-554C is aspirin (ASA). The full chemical designation is 2-(acetyloxy)-benzoic acid with a molecular weight of 180.16 grams/mole. The molecular structure of ASA is shown in ***Figure 1***.

Figure 1: Molecular Structure of Aspirin



Source: NDA Module 2.2

2.2 Tables of Currently Available Treatments for Proposed Indications

ASA is a unique NSAID because of its prolonged effect in inhibiting blood coagulation (4-7 days), compared to other NSAIDs (few hours). NSAIDs are generally administered for pain and fever management, and are usually associated with the treatment of arthritis and other disorders of the musculoskeletal system (Taubert, 2008). ***Table 1*** provides a list of available generic NSAIDS and ***Table 2*** provides a list of brand-only NSAIDs.

Table 1: Generic NSAIDs

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Source: American Society of Health-System Pharmacists

Table 2: Brand NSAIDs

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Source: American Society of Health-System Pharmacists

Table 3 delineates NSAID selectivity towards the cyclooxygenase-1 (COX-1) and cyclooxygenase -2 (COX-2) receptors, respectively. ASA, similar to indomethacin, ketoprofen, piroxicam, and sulindac, has pronounced selectivity toward the COX-1 receptor.

Table 3: NSAID selectivity towards COX-1

Pronounced selectivity towards COX-1	Aspirin Indomethacin Ketoprofen Piroxicam Sulindac
Moderate selectivity towards COX-1	Diclofenac Ibuprofen Naproxen
Equal inhibition of COX-1 and COX-2	Etodolac Meloxicam Nimesulide Nabumetone
Pronounced selectivity towards COX-2	Celecoxib

Source: eMedExpert Home>Comparisons>NSAIDs

ASA is unique in its class for the secondary prevention of cardiovascular events because NSAIDs may increase the probability of myocardial infarction, stroke, and death (Taubert, 2008).

2.3 Availability of Proposed Active Ingredient in the United States

ASA is widely available.

2.4 Important Safety Issues with Consideration to Related Drugs

Table 4 compares the adverse event profile for various NSAIDs. Compared to the general NSAID class, salicylates (i.e. assumed to include ASA) have a minimum effect on the gastrointestinal (GI) and renal systems. ASA is known to cause cerebral and GI bleeding as well as gastric and intestinal ulcers (Taubert, 2008). This table, retrieved from the American Society of Health-System Pharmacists, did not clarify the meaning of platelet adverse event profile. Aspirin clearly has an inhibitory effect on platelets.

Table 4: Comparative Adverse Event Profiles of NSAIDs

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Source: American Society of Health-System Pharmacists (www.ashp.org)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Communication between the Division of Cardiovascular and Renal Products and the Applicant began on December 10, 2009. Advice provided at that time, and reiterated in subsequent communications (i.e. November 18, 2010; November 13, 2012; and January 7, 2013), specified that a study should be designed to define a dose of NHP-554C that pharmacodynamically corresponds to the approved doses of the immediate-release ASA (IR-ASA) formulation. The study should be powered to allow for the estimation of a dose producing 50% inhibition (ID_{50}) of thromboxane (TxA2) with a relative standard error of 20%. Doses of IR-ASA well below 81 mg should be given when comparing this formulation to the NHP-554C formulation because of the near complete inhibition of TxA2 with a dose of 81 mg IR-ASA. The Division also recommended that the Applicant determine both TxA2 and its metabolite, 11-dehydro-TxA2, and to use collagen as an agonist in addition to arachidonic acid for the inhibition of platelet aggregation (IPA) assay. The pharmacodynamic (PD) measures (i.e. TxA2, 11-dehydro-TxA2, and IPA) should be collected following a single dose administration of the ASA products due to its irreversible platelet inhibiting effect and consequent inability to demonstrate a dose-response upon repeated administration. The pivotal protocol (NHP-ASP-01-v1.0) was submitted in the IND on March 28, 2013. From the Minutes of a teleconference dated December 10, 2009, the Applicant was reminded that without clinical outcome studies, they could not claim their product was safer or more effective than IR-ASA. The Applicant acknowledged that their proposed labeling would be the same as the currently marketed products. From correspondence dated August 30, 2013, the Division agreed that the Applicant would not generate an Integrated Summary of Efficacy (ISE) and that all available safety data would be placed in Module 2.7.4 in lieu of an Integrated Summary of Safety (ISS).

2.6 Other Relevant Background Information

There is no other relevant background.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality and integrity was adequate and consistent with agreements made between the Division and the Applicant.

3.2 Compliance with Good Clinical Practices

The study that was conducted by the Applicant to support their NDA (NHP-ASP-01) appeared to be compliant with the principles of Good Clinical Practices as stated in the

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NDA (section 5.2 of the NHP-ASO-01 CSR). The protocol and Informed Consent Form were submitted for approval to an Institutional Review Board (IRB) by the principal investigator.

The principal investigator was Danielle Armas, MD, licensed in Arizona (License # 37416) who was assessed as qualified to perform the study during the 30-day safety review. Sub-investigators listed in Form 1572 were (b) (6) (b) (6). Their curriculum vitae were not included in the IND package. The IRB was (b) (4)

The Informed Consent Form was reviewed and found to be adequate. It informed the subjects about procedures, frequency and total volume of blood to be drawn, potential adverse effects, length of time in the study, and freedom to withdraw without loss of benefits accruable as a research subject. It was also written in a style (i.e. lay language) commensurate with adequate subject comprehension.

3.3 Financial Disclosures

The financial disclosure certificate was reviewed (module 1.3). The Applicant certified that as sponsor of the study, no financial arrangements were entered into with the investigators. Furthermore, the investigators were required to disclose to the Applicant whether there was any propriety interest in the product as defined in 21 CFR 54.2 (a). The Applicant certified that the investigators made no disclosures and that there was no receipt by the investigators of significant payments of other sorts as defined in 21 CFR 54.2 (f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Applicant indicated that NHP-554C capsules were designed as an ASA formulation intended to inhibit circulating Tx (b) (4)
This would be accomplished by (b) (4)

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(b) (4)

I deferred to CMC regarding potential issues associated with the manufacturing process and diffusivity of ASA through the coating agents.

4.2 Clinical Microbiology

No known issues.

4.3 Preclinical Pharmacology/Toxicology

A non-clinical toxicology study in Sprague-Dawley Rats (SDR) was conducted with NHP-554C to assess the toxic effects of this formulation on the GI tract compared to IR-ASA. This was the only safety study reported by the Applicant. The results for IR-ASA and NHP-554C were described and reviewed in the IND (section 8.1.4.3) and presented here in ***Table 5***. For IR-ASA, there were reported toxicological findings, including mortality, with all the doses studied (i.e. 740, 1100, 1670, and 2500 mg/kg). In those rats administered NHP-554C, all animals reportedly survived with no evidence of pathological lesions or clinical signs. The Applicant concluded that the 50% lethal dose (LD_{50}) for IR-ASA was 1432 mg/kg, and that the LD_{50} for NHP-554C was greater than 2500 mg/kg in the SDR model. For the purpose of comparison, the estimated LD_{50} for IR-ASA for various species is shown in ***Table 6***.

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Table 5: Dose limiting toxicities in pre-clinical studies involving the GI tract

Species	Conventional ASA				NHP-554C	
SDR (2 wks)	Dose level for IR- ASA	Toxicity			Dose level for NHP-554C	Toxicity
	740 mg/kg	Mortality (1 M, 1 F)	Hypokinesia, sedation, piloerection, lateral decubitus, dyspnea at all doses.	By Day 7, all surviving animals appeared normal	Not specified (presume same dose range as conventional ASA)	All animals reportedly survived; no clinical signs, no gross pathology. Toxicological studies showed absence of pathological lesions. Single dose of 2500 mpk via oral gavage was reportedly tolerated.
	1110 mg/kg	Mortality (5 F)	All deaths occurred within 3 days post-dose			
	1670 mg/kg	Mortality (1 M, 2 F)	Mortality at 1670 and 2500 mpk showed blackish discoloration of liver, and intestinal and gastric thickening, and red petechiae.			
	2500 mg/kg	Mortality (5 M, 4 F)				
	LD_{50}	1432 mg/kg			>2500 mg/kg	

Source: Applicant's IND, section 8.1.4.3

Table 6: Lethal Doses Producing 50% Mortality for Various Species

Species	LD_{50}
Mouse	250-1300 mpk
Rat	200-2000 mpk
Guinea Pig	1075 mpk
Hamster	3500 mpk
Rabbit	1010, 1800 mpk

Source: Applicant's IND, section 8.2.14. Note: mpk=mg/kg.

The No Adverse Effect Level (NOAEL) and Minimum Anticipated Biological Effect Level (MABEL) were not explicitly provided by the Applicant. The Applicant's proposed dose (i.e. 162.5 mg or approximately 2.3 mg/kg for a 70 kg human) was approximately 10x less than the lowest limit of the oral toxicity range for all the species studied (rat 200 mpk). I deferred to Pharmacology / Toxicology for an in-depth review and assessment.

4.4 Clinical Pharmacology

A brief review of the Applicant's legacy pharmacokinetic (PK) and PD data for NHP-554C activity suggested a delayed attainment of Cmax relative to IR-ASA. Also, there was comparability with IR-ASA in inhibiting serum TxB_2 production for the duration tested as well as comparability with IR-ASA in not significantly inhibiting PGI_2 for the initial 2 weeks. However, after 2 weeks, there was a significant inhibitory effect of IR-ASA on PGI_2, whereas the inhibitory effect of NHP-554C on PGI_2 continued to remain insignificant for the duration of the study (day 21-day 28).

The NHP-ASP-01 trial was the PK/PD pivotal study serving as the basis of the NDA. This was a randomized 4-way cross over single dose, dose response study in healthy volunteers comparing the PK and PD of NHP-554C to IR-ASA. The PK and PD results were consistent with that from legacy studies and showed a dose-dependency for each aspirin congener. I deferred to the Office of Clinical Pharmacology (OCP) for an in-depth review and assessment of the PK/PD data.

4.4.1 Mechanism of Action

NHP-554C is a controlled release aspirin product. The Applicant emphasized that aspirin, known for its prophylactic use against disorders mediated by platelet aggregation and thrombosis such as secondary prevention of acute cardiovascular (CV) events, caused irreversible inhibition of COX-1 that resulted in IPA via inhibition of TxA_2 (beneficial pharmacodynamic effect), however with inhibition of prostacyclin (PGI_2) that promoted clotting (undesired pharmacodynamic effect). The Applicant opined that aspirin-mediated IPA occurred in the portal vein, and PGI_2 inhibition occurred systemically in the post hepatic circulation. The Applicant hypothesized that controlled

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release of ASA would result in deliverance of a low continuous amount of ASA in the intestine sufficient to block platelets in the portal vein from synthesizing TxA_2 but not high enough to saturate liver metabolic mechanisms. Therefore, minimal amounts of ASA would enter the systemic circulation thereby reducing the attenuation of the beneficial effect via reduction in inhibiting PGI_2 (NDA Module 2.5). The result of this mechanism was postulated to enhance the therapeutic index, but was not tested in this NDA.

It was noted that the Applicant referred to both TxA_2 (*Module 2.2 Introduction; Module 2.5 Background section 1.1*) and TxB_2 (*Module 2.7.2 Pharmacodynamic Biomarkers section 1.2.5; Module 2.5 Overview of Clinical Pharmacology section 3.1.4*) as the PD marker serving to establish bioequivalence between NHP-554C and IR-ASA. TxB2 is a byproduct of TxA_2 in the arachidonic acid pathway as shown in ***Figure 2***. I assumed that TxB_2 measurement is an adequate surrogate for TxA_2 (Zhang et al, 2014), but I defer to the OCP to assess the validity of this assumption.

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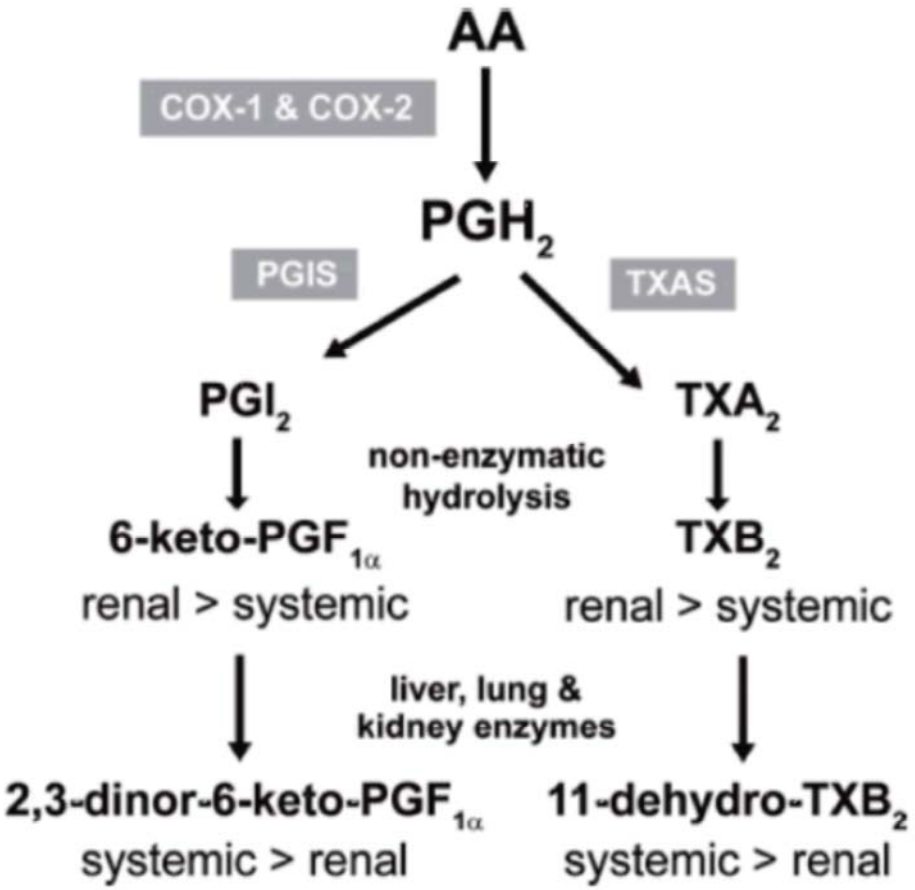
Figure 2: Arachidonic Acid Metabolic Pathway



Source: NDA Module 2.7.2. Note: AA = Arachidonic Acid; COX = cyclooxygenase; PG = prostaglandin; PGIS = prostaglandin I synthase; TXAS = thromboxane A synthase 1.

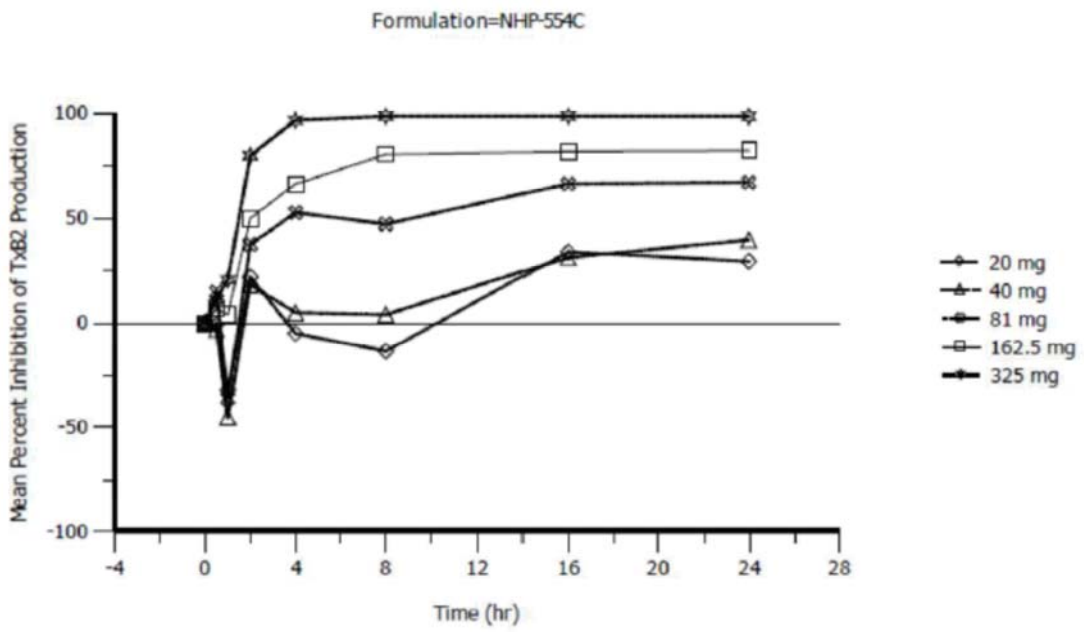
4.4.2 Pharmacodynamics

The PD of ASA and Salicylic Acid (SA) following oral administration of NHP-554C (325 mg) showed a lower degree of TxB2 production inhibition compared to IR-ASA (350 mg) for the first few hours after a single dose (IND, section 3.3 page 23, section 9.4.1.1 page 1435, and section 9.5.1 page 1443). In the CLICR 28 study (i.e. 28-day multiple dose study) comparing NHP-554C 325 mg to IR-ASA 350 mg, the inhibition of TxB_2 reached steady-state on Day 3 for NHP-554C and Day 1 for IR-ASA (greater than 90% TxB_2 production inhibition for both NHP-554C and IR-ASA at steady state). The percent inhibition of TxB_2 production on Day 1 was significantly lower than that achieved during steady state for NHP-554C. Urinary excretion of 6-keto prostaglandin $F_{1\alpha}$, a measure of vascular prostacyclin level, was not significantly reduced following administration of NHP-554C 325mg for the 28 day time-period (from study CLICR 28 report, Figure 5-12,

IND page 203). When administered the IR form of ASA, the urinary excretion of 6-keto prostaglandin $F_{1\alpha}$ was also not significantly reduced for the initial 14 days, after which there emerged a significant reduction from Day 21 to the last measurement at Day 28 (from study CLICR 28 report, Figure 5-13, IND, page 204). These results suggested that both NHP-554C and IR-ASA had a similar PD profile for PGI_2 for the first 2 weeks, after which, as opposed to NHP-554C at 325 mg per day, IR-ASA exerted an inhibitory effect on PG12. However, the potential effect of NHP-554C on PGI_2 inhibition beyond 28 days remained unclear.

The Case Study Report (CSR) of the pivotal NHP-ASP-01 trial showed that single oral doses of NHP-554C (20 mg to 325 mg) and IR-ASA (5mg to 81 mg) inhibited serum TxB_2 production, urine 11-dehydro-TxB2, and platelet aggregation using arachidonic acid as the agonist in a dose-dependent manner. Neither NHP-554C nor IR-ASA inhibited platelet aggregation when collagen was used as the agonist. ***Figure 3*** shows PD data for NHP-554C involving serum TxB_2. Inhibition of serum TxB_2production peaked by 2-4 hours. There was minimal inhibition of serum TxB_2 ($\leq$ 25%) at the 24 hour observation timepoint following NHP-554C single oral doses of 20 mg and 40 mg, respectively. The inhibition of serum TxB_2 production at the 24 hour timepoint following NHP-554C single oral doses of 81 mg, 162.5 mg, and 325 mg were approximately 50%, 75%, and 100%, respectively.

Figure 3: Mean Inhibition of serum TxB2 Production for NHP-554C Doses



Source: NHP-ASP-01 CSR, Figure 9

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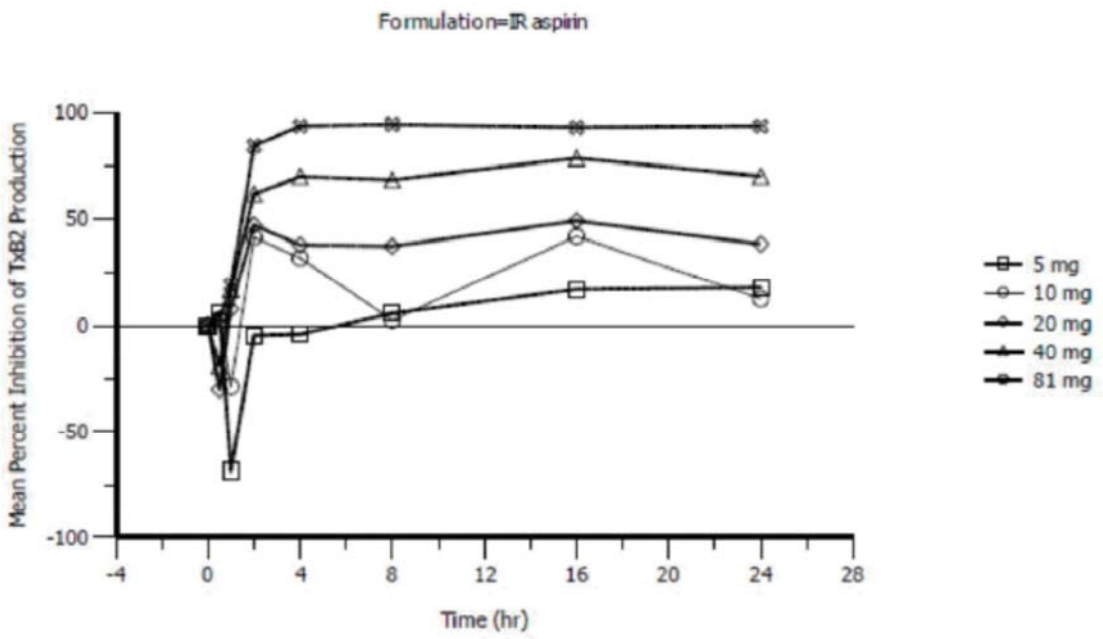
TxB_2 production inhibition data for IR-ASA is shown in ***Figure 4***. There was inhibition of serum TxB2 production at doses of 40 mg (approximately 75%) and 81 mg (approximately 95%). There were lesser degrees of inhibition at doses of 20 mg or less (approximately 50% at 20 mg, approximately 30% at 10 mg; and <25% at 5 mg).

Figure 4: Mean Inhibition of serum TxB_2 Production for IR-ASA Doses



Source: NHP-ASP-01 XSR, Figure 10

Data on IPA from the NHP-ASP-01 study is shown in ***Table 7***. The data is represented as percentage of maximum PD effect (Emax (%)). The table specifies the sample size for each dose of each aspirin congener (N), the mean IPA, the standard deviation (SD), the coefficient of variation (CV%), the minimum, median, and maximum IPA values, the geometric mean and geometric mean coefficient of variation. The NHP-554C doses were 20, 40, 81, 162.5, and 325 mg. The respective mean IPAs were 32, 33, 47, 77, and 99% of Emax (%), respectively. For IR-ASA at doses of 5, 10, 20, 40, and 81 mg, the respective mean IPAs were 23, 15, 30, 46, and 98% of Emax (%). The IPA data suggested that the NHP-554C dose of 325 mg and the IR-ASA dose of 81 mg showed similar IPA effects.

The NHP-ASP-01 study did not collect prostacyclin samples in order to confirm the low rate of PG12 inhibition for NHP-554C relative to IR-ASA that was observed in at least one legacy study.

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Table 7: Summary of IPA following single oral doses of NHP-554C or IR-ASA

		Dose (mg)						
		5.0	10.0	20.0	40.0	81.0	162.5	325.0
Formulation	Descriptive Statistics	E_{max} (%)						
NHP-554C	N	NA	NA	20	18	17	17	19
	Mean	NA	NA	32	33	47	77	99
	SD	NA	NA	32	31	38	37	0.76
	CV%	NA	NA	100	93	82	48	0.77
	Min	NA	NA	0.0	0.0	4.0	6.8	98
	Median	NA	NA	20	20	30	98	100
	Max	NA	NA	100	93	100	100	100
	Geometric Mean	NA	NA	NC	NC	29	59	99
	CV% Geometric Mean	NA	NA	NC	NC	170	110	0.77
IR Aspirin	N	20	17	20	20	16	NA	NA
	Mean	23	15	30	46	98	NA	NA
	SD	24	8.0	34	39	2.8	NA	NA
	CV%	110	54	110	85	2.9	NA	NA
	Min	0.0	0.0	0.0	0.0	91	NA	NA
	Median	15	16	14	24	100	NA	NA
	Max	91	29	100	100	100	NA	NA
	Geometric Mean	NC	NC	NC	NC	98	NA	NA
	CV% Geometric Mean	NC	NC	NC	NC	2.9	NA	NA

NC = Not calculable.
NA = Not applicable.
Source: Table 14.2.20
Source: NHP-ASP-01 CSR, Table 16

4.4.3 Pharmacokinetics

Maximum concentrations of ASA and SA after NHP-554C administration were generally less than 20% of those observed with an IR or enteric-coated (EC) form. The Cmax occurred at a later point in time for NHP-554C (Tmax = 0.71, dose 325 mg, study PKCR, 0491) compared to the IR formulation (Tmax = 0.50, dose 350 mg, study PKCR 0491). Food delayed the onset of NHP-554C absorption by 1-2 hours, but not the rate of absorption. The bioavailability of ASA upon NHP-554C administration was approximately 20% greater with food relative to the fasted state. The PK results showing a delay in Cmax for NHP-554C 350 mg compared to IR-ASA and EC-ASA were consistent with the expected release patterns of the controlled release formulation.

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5 Sources of Clinical Data

There were 15 clinical trials evaluating NHP-554C that were reported by the Applicant, and are listed in Appendix 9.1. Of these, 8 studies evaluated PK/PD, 3 studies evaluated GI toxicity and tolerability, 1 study evaluated analgesia, and 3 studies evaluated NHP-554C in patients with atherosclerosis (i.e. U5A-96-02-002, U5A-98-02-004, and CLICR 29). With the exception of the three studies in subjects with atherosclerosis, all other studies were conducted in healthy volunteers. All the studies with the exception of NHP-ASP-01 were legacy studies that were conducted in the 1990s.

5.1 Tables of Studies/Clinical Trials

Table 8 shows the number of subjects, doses of NHP-554C, and duration of treatment for each of the 15 trials. A total of 819 subjects were exposed to NHP-554-C at various doses for various periods of time. In 6 of the trials, a total of 279 subjects were administered a single dose of NHP-554C. In one of the trials, a total of 44 subjects were administered NHP-554C for less than 1 week. In 3 trials, a total of 61 subjects were administered NHP-554C for a duration of 1-2 weeks. Subjects were administered NHP-554C for 3 weeks in 1 trial (n=48), 4 weeks in 2 trials (n=45), and 6 weeks in 2 trials (n=223). In one trial (CLICR 29), the NHP-554C exposure time was planned for 13 months but actual exposure time varied up to 7 months (n=119). Based on the legacy studies, the Applicant's proposed doses were studied for relatively longer periods of time with relatively larger sample sizes.

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Table 8: NHP-554C Clinical Trials: Sample Size, Dose, and Duration of Treatment

Study	Number of Subjects on NHP-554C (ITT)	Dose of NHP-554C (mg)	Treatment Duration
NHP-ASP-01	20	20	Single Dose
NHP-ASP-01	19	40	Single Dose
NHP-ASP-01	18	81	Single Dose
NHP-ASP-01	18	162.5	Single Dose
PKFT 9542	50	162.5	Single Dose
NHP-ASP-01	20	325	Single Dose
ASA-001	50	325	Single Dose
PKCR 0491	12	325	Single Dose
PKFT 97101	24	650	Single Dose
PKFT 97101	24	975	Single Dose
CLFT 102-9001	24	975	Single Dose
CLFT 103-9802	22	650	5 Days
CLFT 103-9802	22	1300	5 Days
ASA-002	25	325	7 Days
CLICR 30	12	162.5	10 Days
PKFT 97101	24	325	13 Days
U5A-96-02-001	24	162.5	21 Days
U5A-96-02-001	24	325	21 Days
CLICR 28	13	325	28 Days
U5A-96-02-002*	32	162.5	28 Days
U5A-98-02-004*	186	162.5	6 Weeks
U5A-97-02-003	37	162.5	6 Weeks
CLICR 29*	119	325	Up to 7 Months

*Source: Compiled data from NDA as shown in Appendix 9.1. ITT= Intention to Treat; *patients with atherosclerotic disease.*

The data was re-arranged to display the number of subjects taking NHP-554C at various doses as a function of time, and is shown in ***Table 9***. Over the last 2 decades, the dose-time exposure of the 819 subjects ranged from 20 mg to 1300 mg for durations ranging from a single dose to up to 7 months. The greatest exposure occurred for the 162.5 mg dose (n=359) and the 325 mg dose (n=287). Of the 359 subjects receiving 162.5 mg NHP-554C, 68 received a single dose, 12 received daily doses for 1-2 weeks, 24 received daily doses for 3 weeks, 32 received daily doses for 4 weeks and 223 received daily doses for 6 weeks. Out of the 287 subjects receiving NHP-554C 325 mg, 82 received a single dose, 49 received daily doses for 1-2 weeks, 24 received daily doses for 3 weeks, 13 received daily doses for 4 weeks, and 119 received daily doses for up to 7 months.

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Table 9: NHP-554C Exposure Experience for each NHP-554C Dose

Dose (mg)	Number of Subjects exposed to NHP-554C	Number of subjects on each dose for specific time periods						
		Single Dose	< 1 week	1-2 weeks	3 weeks	4 weeks	6 weeks	Up to 7 months
20	20	20	---	---	---	---	---	---
40	19	19	---	---	---	---	---	---
81	18	18	---	---	---	---	---	---
162.5	359	68	---	12	24	32	223	---
325	287	82	---	49	24	13	---	119
650	46	24	22	---	---	---	---	---
975	48	48	---	---	---	---	---	---
1300	22	---	22	---	---	---	---	---
Total	819	279	44	61	48	45	223	119

Source: Re-arrangement of data from Table 8 of this review

5.2 Review Strategy

The review strategy focused on a safety evaluation via reported adverse events from all the legacy studies and the pivotal PD study. NHP-554C was compared to IR-ASA as a function of dose and duration based on trials listed in ***Table 8*** and derived exposure data listed in ***Table 9***. Adverse events from each of the trials were tabulated and pooled by system organ class (SOC). MedDRA version 16 was used to assign adverse events to SOCs.

> *Reviewer comment: I felt that integrating adverse events from legacy trials conducted in the 1990s with adverse events in the pivotal PD study conducted in 2013 might have been impacted by a changing standard of care. I also recognized that lumping trials that enrolled healthy subjects with those that enrolled subjects with atherosclerosis might have impacted safety data interpretation. However, this procedure was thought to enhance the possibility of signal detection. Particular attention was given to the GI system in order to determine the existence of any safety issues as a consequence of continued ASA release downstream in the GI tract.*

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Without efficacy data in this NDA and as per the pre-submission agreement with the Applicant, there were no efficacy or safety claims relative to marketed product. With the exception of NHP-ASP-01 and ASA-001, the CSRs were not accompanied by datasets. This review therefore relied on data tabulations that were placed into the legacy CSRs.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 NHP-ASP-01

NHP-ASP-01 was a Phase 1 randomized open label four-way crossover single dose, dose-response study comparing the PD and PK of NHP-554C capsules to IR-ASA capsules in 50 healthy volunteers (USA, 2013). The doses of NHP-554C were 20 mg, 40 mg, 81 mg, 162.5 mg, and 325 mg. The doses of IR-ASA were 5 mg, 10 mg, 20 mg, 40 mg, and 81 mg. The design strategy involved each subject randomized to receive four separate single doses of study drug (2 separate doses of NHP-554C, and 2 separate doses of IR-ASA) each followed by a 2-week washout period.

The data was compiled from the Treatment Arm (ta.xpt) and Adverse Event (ae.xpt) datasets and analyzed in JMP. The data is shown in Appendix 9.2. The review of the dataset showed general consistency with tables appearing in the CSR although there were some inconsequential inconsistencies. For example, the dataset showed 5 adverse events in the NHP-554C 40 mg arm, whereas the CSR (Table 17) specified only 2 adverse events, both of them mild. There were 8 (by dataset) vs. 7 (by CSR Table 17) adverse events in the NHP-554C 162.5 mg arm. Similarly, there were 12 (by dataset) vs. 13 (by CSR Table 18) adverse events in the IR-ASA 5 mg arm. There were 2 (by dataset) vs. 3 (by CSR Table 18) adverse events in both the IR-ASA 10 mg and 20 mg arms, respectively. The dataset showed 1 adverse event in the IR-ASA 81 mg arm, whereas the CSR Table 18 specified no adverse event in that arm. There was agreement between the dataset and CSR tables for the NHP-554C 20 mg arm and 325 mg arm, as well as the IR-ASA 40 mg arm. The review of the adverse event profile for this trial was based on the datasets rather than what appeared in the CSR.

For all NHP-554C doses, there were 25 adverse events. For all IR-ASA doses, there were 18 adverse events. There was no empirical dose-dependency for adverse events in either the NHP-554C or IR-ASA formulations. Most of the reported adverse events (abdominal pain, diarrhea, eructation {GI}; chills, feeling hot, pruritus at venipuncture site {General}; postural dizziness, headache {Nervous disorder}, nasal congestion, cough, rhinorrhea {Respiratory}) were assessed by the investigator as being mild. There was no apparent SOC cluster of adverse events. No signal emerged from this study. There was one adverse event described as liver function elevation that was reviewed in detail (see section 7.3.5 of this NDA clinical review).

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5.3.2 PKFT 9542

PKFT 9542 was a Phase 1 randomized open label, 2-way crossover single dose study conducted in 24 healthy volunteers (France, 1996).This study was designed to evaluate the PK parameters of two formulations of NHP-554C after a single oral dose of 162.5 mg. Based on the CSR, no clinical adverse were reported.

5.3.3 ASA-001

ASA-001 was a Phase 1 open label 3-treatment, 3 period, 6 sequence crossover study evaluating comparative bioavailability and food effect between a single dose of NHP-554C (325 mg) and a single dose of IR-ASA (325 mg) in 26 healthy volunteers (USA, 1997). Safety data are shown in Appendix 9.4. There were no deaths and no serious adverse events (SAE).

In the NHP-554C Fasted State arm, there were 6 reported adverse events categorized as mild-to-moderate. Four of these adverse events were reported as “body as a whole” (i.e. clinically judged as General). One adverse event was reported as metabolic/nutritional disorder and one subject had ear pain.

In the NHP-554C Fed State arm, there were 5 reported adverse events (i.e. 3 “body as a whole” clinically judged as General; 1 phlebitis mapped to the Vascular SOC; and 1 dyspepsia mapped to the GI SOC).

In the IR-ASA Fed State arm, there were 5 reported adverse events (i.e. 3 “body as a whole” mapped to General; 1 anorexia mapped to GI; and 1 heme/lymphatic event due to ecchymosis that was mapped to the Blood and Lymphatic SOC).

There were no reported adverse events in the IR-ASA Fasted State arm.

5.3.4 PKCR 0491

PKCR 0491 was a Phase 1 open label 3-way crossover study designed to compare the PK of NHP-554C (325 mg) vs. ASPEGIC (aspirin 350 mg) after a single dose oral administration in 12 healthy volunteers (France, 1992). The CSR specified that “no serious clinical indisposition or undesirable effect requiring emergency treatment or discontinuation of the study was recorded” (CSR section 4.5). The CSR did not specify any adverse events.

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5.3.5 PKFT 97101

PKFT 97101 was a Phase 1 randomized open-label 4-sequence crossover PK/PD study comparing various loading doses (650 and 975 mg) and maintenance doses of NHP-554C vs. IR-ASA in 24 healthy volunteers (France, 1997). Treatment periods were in 4-5 day cycles. There were 4 treatment regimens to which the subjects were randomized: **A)** NHP-554C 325 mg or IR-ASA 325 mg from Day 1 to Day 5; **B)** NHP-554C 650 mg on Day 1 followed by NHP-554C 325 mg from Day 2 to Day 5, or IR-ASA 650 mg on Day 1 followed by IR-ASA 325 mg from Day 2 to Day 5; **C)** NHP-554C 975 mg on Day 1 followed by NHP-554C 325 mg from Day 2 to Day 5, or IR-ASA 750 mg on Day 1 followed by IR-ASA 325 mg from Day 2 to Day 5; **D)** UPSA Aspirin gelatin capsule 325 mg or IR-ASA 325 mg from Day 1 to Day 5. All 24 subjects were randomized to all 4 treatment regimens in various sequences.

The CSR specified that “none of the subjects presented any serious adverse events during the trial. One subject presented with a non-serious adverse event during the trial: erythematous angina, 24 hours after the fifth intake of treatment A”. The subject was treated with Rulid. A search of this term led to a diagnosis of genital chlamydia trachomatis. Rulid is the macrolide antibiotic roxithromycin. The “fifth intake of treatment A” meant that the subject was either on NHP-554C 325 mg, or IR-ASA 325 mg. Because the CSR did not specify what study drug the subject was taking at the time of the adverse event despite being non-attributable to study drug, this adverse event was assigned to the NHP-554C arm and mapped to Infection as shown in Appendix 9.6.

5.3.6 CLFT 102-9001

CLFT 102-9001 was a randomized, double-blind, double-dummy, placebo and reference-controlled, single oral dose 4-way crossover study designed to test the time-efficacy relationship of the analgesic effect of NHP-554C compared to IR-ASA and placebo in 24 healthy volunteers (Germany, 2000). The NHP-554C dose was 975 mg, and the IR-ASA dose was 500 mg. Naproxen 220 mg was the reference control. The analgesic effect was measured by visual analogue scales post-ultraviolet irritated skin on the subject’s back.

The CSR specified that there were 27 adverse events, no deaths and no other serious adverse events (placebo: 4; NHP-554C: 3; IR-ASA: 14; and Naproxen: 6). The adverse events were reported as headache (mapped to Nervous SOC), nausea and gastrointestinal trouble (mapped to GI SOC), cold (mapped to Infection SOC), irritability and changes in mood (mapped to General SOC as it was judged not to be a psychiatric issue). Safety issues were manually tabulated and are shown in Appendix 9.7.

5.3.7 CLFT 103-9802

CLFT 103-9802 was a double-blind, dose response, 4-way crossover study in 23 healthy volunteers (UK, 1999-2000). The study was designed to define a dose-response relationship of ASA-induced GI toxicity and to determine if NHP-554C afforded a protective effect compared to IR-ASA. Doses studied were NHP-554C 650 mg once daily for 5 days, IR-ASA 600 mg and 1200 mg respectively once daily for 5 days.

A Statistical Study Report was submitted in the NDA in lieu of a CSR. There were no conclusions drawn in the Statistical Study Report. The report specified 3 gastric/duodenal erosions during the IR-ASA 600 mg treatment period, 2 during the NHP-554C 650 mg treatment period, 1 during the NHP-554C 1300 mg treatment period, and 1 during another IR-ASA 600 mg treatment period. The report stated that the presence of gastric and duodenal erosions was impacted by a sequence effect, whereby the erosions from an antecedent drug regimen were still active during initiation of the next drug regimen in the crossover design.

There were 19 adverse events reported by system organ class: 4 Nervous System, 7 Gastrointestinal, 5 Respiratory System, and 1 each in Renal/Urinary, Reproductive, and General, respectively. Information about the study drug administered at the time of the adverse events, as well as whether any of the events were SAEs, was not available. Consequently, all reported adverse events were arbitrarily attributed to the NHP-554C 1300 mg dose. The manual tabulation of the adverse events is shown in Appendix 9.8.

5.3.8 ASA-002

ASA-002 was a randomized multiple dose, steady state open-label crossover study comparing NHP-554C to a delayed release aspirin (Ecotrin®). The study was designed to evaluate the PK/PD effect for each aspirin formulation. NHP-554C 325 mg and Ecotrin® 325 mg were administered once daily for 7 days in 25 healthy volunteers (USA, 1997).

A CSR was not submitted in the NDA. In lieu of a CSR, module 5.3.1.2 contained a PD report, an analytical PD report, as well as tables and listings that provided adverse events by SOC. There were 12 adverse events in the NHP-554C arm and 6 adverse events in the Ecotrin® arm. Six of the 25 subjects in the NHP-554C arm reported one or more adverse events, whereas 3 of the 24 subjects in the Ecotrin® arm reported one or more adverse events. There were no reported SAEs. The adverse events, all classified as mild, were in the Respiratory, Gastrointestinal, Cardiovascular, and General SOCs, the latter system showing an imbalance (7 vs 0) of events against NHP-554C (i.e. pain, headache, asthenia, and accidental injury). There was one cardiovascular adverse event (“syncope”) and one gastrointestinal adverse event (“increased salivation”), both in the Ecotrin® arm. The respiratory adverse events (NHP-554C: 5 vs. Ecotrin®: 4) included “cough increased” (NHP-554C: 1 vs. Ecotrin®: 2), “lung disorder” (NHP-554C:

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0 vs. Ecotrin®: 1), “pharyngitis” (NHP-554C: 2 vs. Ecotrin®: 1), and “rhinitis” (NHP-554C: 2 vs. Ecotrin®: 0). The manually derived table of adverse events is shown in Appendix 9.9.

5.3.9 CLICR 30

CLICR 30 was a randomized, open label multiple dose crossover study comparing NHP-554C 162.5 mg vs. IR-ASA 160 mg administered once daily for 10 days in 12 healthy volunteers (France, 1994). Only 1 adverse event was reported in the IR-ASA arm described as a hematoma associated with a catheter insertion in the left arm of subject # 8. This singular event was recorded in tabular format under the Surgical and Medical Procedures category and is shown in Appendix 9.10.

5.3.10 U5A-96-02-001

U5A-96-02-001 was a double-blind crossover comparison of the effects of a high dose regimen: NHP-554C (325 mg) vs. enteric-coated IR-ASA (325 mg), to the effects of a low dose regimen: NHP-554C (162.5 mg) vs. enteric-coated IR-ASA (75 mg), on gastroduodenal mucosa as assessed endoscopically in 48 healthy volunteers (24 randomized to the high dose regimen and 24 randomized to the low-dose regimen) (UK, 1996-1997). Study drug treatment continued for 3 weeks.

With respect to endoscopic results, the CSR reported no detected ulcers following treatment with NHP-554C (325 mg) or enteric-coated IR-ASA (75 mg). One ulcer was detected in the gastric antrum of one subject after 21 days of treatment with enteric-coated IR-ASA (325 mg) and one was detected in the gastric antrum of each of 2 subjects at 7 and 14 days after treatment with NHP-554C (162.5 mg).

After 21 days of treatment, a total of 16 of 23 subjects in the NHP-554C (325 mg) group were reported to have endoscopic evidence of erosions, 7 of which were hemorrhagic. A total of 20 of 24 subjects were reported to have erosions on endoscopy in the enteric-coated IR-ASA (325 mg) group, 10 of which were hemorrhagic. Similarly, 22 of 23 subjects were reported to have endoscopic evidence of erosions in the NHP-554C (162.5 mg) group, 8 of which were hemorrhagic; and 16 of 23 subjects were reported to have endoscopic evidence of erosions in the enteric-coated IR-ASA (75 mg) group, 5 of which were hemorrhagic. The detected ulcers were included in the counting of erosions.

The CSR stated that at the end of the 21 day study, the number of hemorrhagic erosions was 2.91 per subject in the enteric-coated IR-ASA (325 mg) group, 0.30 per subject in the NHP-554C (325 mg) group, 0.35 per subject in the NHP-554C (162.5 mg) group, and 0.13 per subject in the enteric-coated IR-ASA (75 mg) group.

The authors of the CSR concluded that NHP-554C produced significantly less upper GI damage than the equivalent dose of conventional aspirin. All 4 groups produced low

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levels of GI damage over 3 weeks, the lowest in the enteric-coated IR-ASA (75 mg) group. (*Reviewer Comment*: (b) (4)

(b) (4)

The CSR specified no SAEs, deaths, or adverse events causing withdrawal in either the high dose or low dose treatment groups. The CSR specified that a total of 8 volunteers experienced 14 non-serious adverse events in the high dose regimen arm, and 7 subjects experienced 9 non-serious adverse events in the low dose regimen arm. These adverse events were described as upper respiratory tract infections (URI), rhinitis, headaches, diarrhea, urinary tract infection (UTI), purpura, infection, accidental injury, and abdominal pain. In the high dose regimen, Subject UK001-13 experienced URI in two separate time periods and therefore they were recorded as separate adverse events. Similarly in the high dose regimen, Subject UK001-14 experienced "headache" on 2 separate occasions and therefore they were recorded as separate adverse events. All adverse events were assessed by the study investigator as being mild, with the exception of the accidental injury in the low dose regimen arm that was listed as moderate in severity.

In this NDA review, UTI was mapped to Renal and Urinary disorders, and both diarrhea and abdominal pain were mapped to the Gastrointestinal SOC. Headache was mapped to Nervous System, purpura was mapped to Vascular Disorders, and both URI and rhinitis were mapped to Respiratory Disorders. The tables in the CSR allocated these adverse events to either the high dose regimen or low dose regimen. Within each regimen, there was no sub-allocation to either NHP-554C or enteric-coated IR-ASA. Therefore, the adverse events in this study were arbitrarily attributed to NHP-554C in each regimen. These adverse events were manually tabulated and are shown in Appendix 9.11.

5.3.11 CLICR 28

CLICR 28 was a randomized multiple-dose, open label crossover study comparing NHP-554C 325 mg vs. IR-ASA 350 mg administered once daily for 28 days in 13 healthy volunteers (France, 1992-1993).

There was 1 adverse event described as "severe traumatism of the left shoulder on Day 4 of the second period of the study requiring treatment with floctafenine and naproxen. After contact with the monitor, the subject is maintained in the trial. No other intercurrent event was recorded". It was not clear what study drug this subject was taking at the time of the adverse event. It was therefore attributed to NHP-554C and categorized in Appendix 9.12 in the Injury SOC.

5.3.12 U5A-96-02-002

There was a naming mismatch in the NDA regarding this study. The CSR for this legacy study was named U5A-97-06-002 rather than U5A-96-02-002. No other errors regarding study titles were noted upon review. This study was referred to as U5A-96-02-002 in order to remain consistent with the Applicant's NDA package.

U5A-96-02-002 was a single blind, parallel group comparison of three dosage forms of aspirin on antiplatelet activity in patients with a history of atherosclerotic disease. All subjects received enteric-coated IR-ASA 75 mg once daily for at least 14 days. They were subsequently randomized to receive once-daily doses of either NHP-554C 162.5 mg (n=32), or enteric-coated IR-ASA 150 mg (n=32), or enteric-coated IR-ASA mg 75 mg (n=34) for 28 days (UK, 1996-1997). The efficacy endpoint was platelet aggregation and release of 5-hydroxytryptamine (5-HT).

A brief review of the efficacy data showed that NHP-554C 162.5 mg and enteric-coated IR-ASA 150 mg could be differentiated from enteric-coated IR-ASA 75 mg by their effect on thromboxane levels and platelet activity. Empirical similarity between NHP-554C 162.5 mg and enteric-coated IR-ASA 150 mg in IPA was questionable because of baseline imbalance.

SAEs were reported for 10 subjects, 6 during the trial (5 hospitalizations and 1 cancer) and 4 during the 30 days following completion of study drug treatment (3 deaths and 1 hospitalization). Of the 6 SAEs during the trial, none were in the NHP-554C group. Two of these SAEs (1 hospitalization and 1 cancer) were in the IR-ASA 150 mg group and 4 (all hospitalizations) were in the IR-ASA 75 mg group. There were no deaths during the study period. In the post-study period, 2 of the 4 SAEs had been in the IR-ASA 75 mg group (hospitalization and death), 1 had been in the IR-ASA 150 mg group (death) and 1 had been in the NHP-554C group (death). A brief description of the SAEs is provided herewith:

<u>SAEs during Study Drug Treatment</u>

- Patient # 13 (IR-ASA 75 mg): age/gender unspecified. Hospitalization due to exacerbation of COPD.
- Patient # 32 (IR-ASA 75 mg): 71 year old (y/o) male hospitalized for routine cardiac catheterization.
- Patient # 102 (IR-ASA 75 mg): 77 y/o female hospitalized for "vagueness" presumed by the Investigator to have been a transient ischemic attack (TIA). The patient was discharged without a definitive diagnosis.
- Patient # 92 (IR-ASA 75 mg): 65 y/o male hospitalized for routine angiogram.
- Patient # 104 (IR-ASA 150 mg): 69 y/o male hospitalized for routine cardiac catheterization.

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- Patient # 118 (IR-ASA 150 mg): 58 y/o male diagnosed with Myelogenous Leukemia.

SAEs Post Study

- Patient # 89 (IR-ASA 75 mg): 48 y/o female hospitalized for bradycardia and angina 14 days post last dose of study drug.
- Patient # 107 (IR-ASA 75 mg): 60 y/o patient (gender not specified) died consequent to subarachnoid hemorrhage 11 days post last dose of study drug.
- Patient # 54 (IR-ASA 150 mg): 76 y/o male died consequent to acute coronary syndrome 10 days post last dose of study drug.
- Patient # 57 (NHP 162.5 mg): 58 y/o male who experienced sudden death 3 weeks post last dose of study drug. No other explanation.

There was a listing of treatment-emergent adverse events: nausea, vomiting, diarrhea, and dyspnea (all mapped to the Gastrointestinal SOC); rhinitis, coughing, and dyspnea (all mapped to the Respiratory SOC); rash, skin disorder (all mapped to the Skin SOC); headache, paresthesia (all mapped to the Nervous System SOC); abscess (Infection SOC); angina pectoris (Cardiac SOC); dizziness (Vascular SOC); hypokalemia (Metabolism SOC); vertigo (Ear and Labyrinth SOC); myalgia (Musculoskeletal SOC); “thinking abnormal” (Psychiatric SOC); and others where the term readily reflected the SOC to which it was mapped (i.e. eye abnormality, infection, renal pain, and previously scheduled surgery).

In summary, there were 14 adverse events in the NHP-554C arm (1 of them an SAE), 14 adverse events in the IR-ASA 150 mg arm (3 of them SAEs), and 29 adverse events in the IR-ASA 75 mg arm (6 of them SAEs). The data is displayed in Appendix 9.13.

5.3.13 U5A-98-02-004

U5A-98-02-004 was a Phase 3 randomized multi-center double-blind parallel group trial that compared the tolerability of NHP-554C 162.5 mg to IR-ASA 150 mg in patients with atherosclerosis following 6 weeks of study drug treatment (UK, 1999-2000).

The CSR provided by the Applicant appeared to be a template devoid of relevant study information with the exception of a section describing sample size estimation, disposition of subjects, and safety tables emphasizing GI toleration.

Subject disposition is shown in ***Figure 5***. Of the 186 subjects randomized to the NHP-554C arm, 134 completed the 6 week study. Of the 196 subjects randomized to the IR-ASA arm, 143 completed the 6 week study. Fifty subjects (with 2 additional subjects apparently lost to follow-up) were reported to have withdrawn from the NHP-554 arm. Of these, 27 were reported to have withdrawn consequent to adverse events. Fifty-two subjects (with 1 additional subject apparently lost to follow-up) were reported to have

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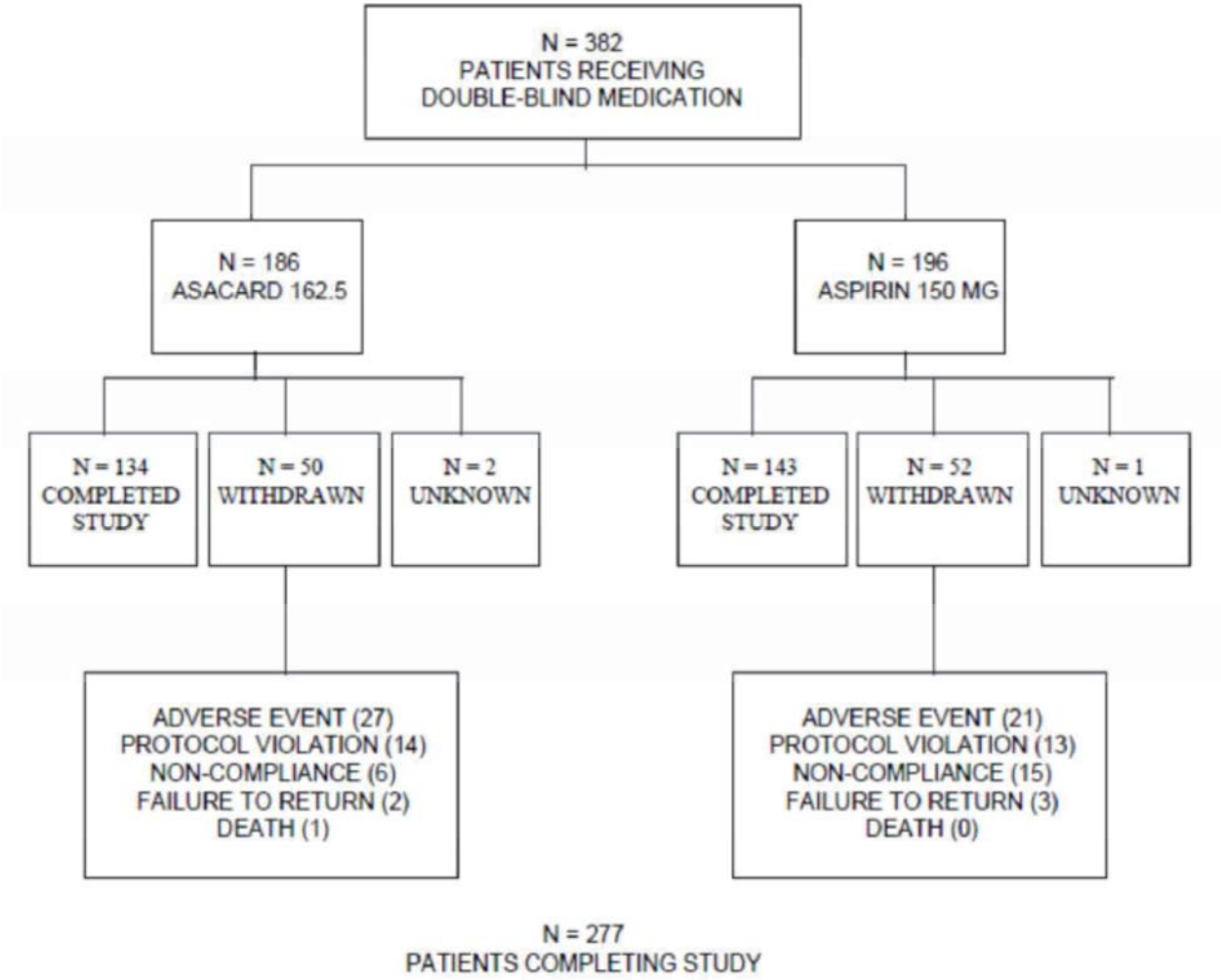
withdrawn from the IR-ASA arm. Of these, 21 were reported to have withdrawn consequent to adverse events. Subject disposition was generally balanced between the arms.

Figure 5: Subject Disposition in Study U5A-98-02-004



Source: U5A-98-02-004 CSR, Figure 8a

The authors of the CSR summarized the incidence of GI tolerability complaints that were recorded in subject diaries during the course of the trial and are shown in ***Table 10***. The authors represented the data as percentage of subjects in each arm registering the complaint. The intolerance variables included “GI Discomfort”, “Nausea”, “Indigestion/Heartburn”, “Abdominal Pain”, “Vomiting”, and “Rap-eze”. With the exception of “GI Discomfort”, all descriptive intolerance variables were experienced at a slightly higher percentage in the NHP-554C group. The term “Rap-eze” was presumed

to be calcium carbonate likely associated with GI discomfort as the cause of its administration. It was not clear from the CSR if there were sufficient definitional distinctions between each term, and if so, how well the subjects in the trial were instructed regarding data entry into the diary. The CSR did not discuss potential definitional overlap or variability consequent to subjectivity.

Table 10: Study U5A-98-02-004: Incidence of Diary Based GI Tolerability

	Asacard 162.5	Aspirin 150 mg	Absolute Reduction (a)	Relative Reduction (b)
GI Discomfort	51.3%	57.9%	6.6%	11.4%
Nausea	54.6%	46.3%	8.3%	15.5%
Indigestion/ Heartburn	54.6%	48.2%	6.4%	12.4%
Abdominal Pain	52.6%	45.7%	6.9%	12.7%
Vomiting	55.9%	49.4%	6.5%	12.8%
Rap-eze	57.2%	49.4%	7.8%	15.4%

(a) absolute reduction = percentage on Aspirin minus percentage on Asacard.

(b) relative reduction = absolute reduction / percentage on Aspirin.

Source: U5A-98-02-004 CSR, Table 3. Note that based on the formula, negative numbers were expected to be recorded when the percentage of patients with a symptom on aspirin was lower than that on Asacard.

The incidence of GI tolerability complaints entered into the diary spanned the duration of the 6 week trial. The percentage of subjects in the trial that recorded GI complaints during discreet time periods is shown in ***Table 11***.

Table 11: U5A-98-02-004: Tolerability Complaints for Specific Trial Durations

Days %	GI Discomfort %		Nausea %		Indigestion Heartburn %		Abdominal Pain %		Vomiting %		Rap-eze %	
	NHP	IR	NHP	IR	NHP	IR	NHP	IR	NHP	IR	NHP	IR
None	49	42	55	46	55	48	53	46	56	50	57	49
1-10	19	22	18	20	19	18	19	19	20	18	19	18
11-25	12	12	12	12	13	12	12	13	12	13	12	14
26-50	11	9	8	11	7	11	10	10	7	10	6	10
51-100	9	15	8	11	7	10	7	12	6	10	6	9

Source: manual data compilation from tables and listings in the U5A-98-02-004 CSR, Tables 5-10

Regarding "GI Discomfort", 49% of the subjects in the NHP-554C arm and 42% of the subjects in the IR-ASA arm of the study did not register any complaints (i.e. complaints were recorded in 0% of the days). Of the subjects in the trial, 9% in the NHP-554C arm and 15% in the IR-ASA arm recorded "GI Discomfort" for a total of 51-100% of the days in the study. Regarding "Vomiting", 56% of the subjects in the NHP-554C arm and 50% of the subjects in the IR-ASA arm did not register any complaints. However, 6% of the subjects in the NHP-554C arm and 10% of the subjects in the IR-ASA arm recorded complaints of vomiting for 51-100% of the days in the study. It was not clear if a subject entered more than one complaint during the same or different time periods. Despite the lack of evidence to control variability while deploying a subjective process, subjects were blinded when entering data into their diaries thereby attenuating bias. Based on the GI tolerability diary data, approximately half of the subjects registered no complaints for 1-10% of the days in the trial. Approximately 12% of the subjects registered complaints for 11-25% of the days in the trial, and approximately 9% of the subjects entered complaints for both 26-50% and 51-100% of the days in the study. The distribution of complaints between the arms of the study appeared to be generally similar to each other although for those who complained for greater than 50% of the time in the trial, there was a noticeable trend for a greater incidence of complaints in the IR-ASA arm compared to the NHP-554C arm.

A review and compilation of the adverse event listing is shown in Appendix 9.14. There were 66 adverse events in the NHP-554C arm and 72 adverse events in the IR-ASA arm. In the CSR tables, the severity of the adverse events was listed only for the Gastrointestinal SOC. Based on a manual review, there were 3 adverse events classified as Gastrointestinal SOC in the NHP-554C arm. There were 13 adverse events classified as Gastrointestinal SOC in the IR-ASA arm. In the IR-ASA arm, the content verbiage in the CSR specified 14 adverse events in that SOC. I speculated that the term "H Pylori", which was classified in this review as Infection, may have been

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classified as Gastrointestinal by the authors of the CSR. There was also 1 SAE (vomiting/hematemesis) that was described in the CSR content but not listed in the table of adverse events. This might have been the 14th adverse event rather than a classification difference of the "H Pylori" event. Alternatively, one of the diary entries recorded as "vomiting" might have been the 14th adverse event. However, it did not appear that events recorded in subject diaries were categorically included in the adverse event listing.

There were 6 SAEs in the NHP-554C arm (death, transient ischemic attack, breast cancer, myocardial infarction, syncope, and admission for cardiac catheterization). There were 5 SAEs in the IR-ASA arm (myocardial infarction, angina pectoris, bright red blood per rectum, vomiting/hematemesis, and "circumcision balanitis erotica obliterans"). The death in the NHP-554C arm was a case of a 90 year old male with a history of diabetes, cataracts, incontinence, and atherosclerosis. Three days after receiving his first dose of NHP-554C, he had a "fall" for unknown reasons. This was described in the CSR text as a severe SAE. The CSR data table listed "syncope" as a SAE and it was presumed following a review that syncope was the "fall". The term "syncope" was mapped to the Cardiovascular SOC. Three weeks later, the subject died. The authors of the CSR attributed the death to old age and Alzheimer's disease, despite the latter not mentioned in the medical history.

Regarding the totality of the data in this Phase 3 trial in patients with atherosclerosis, there was no observable safety signal concerning NHP-554C.

5.3.14 U5A-97-02-003

U5A-97-02-003 was a Phase 2, randomized, double blind, placebo controlled, double-dummy, parallel group six week single center trial that compared the effects of NHP-554C 162.5 mg to IR-ASA 150 mg on gastrointestinal mucosal injury assessed endoscopically in healthy volunteers (UK, 1997-1998).

A total of 114 volunteers were randomized to receive NHP-554C (n=37) or IR-ASA (n=40) or placebo (n=37) for a total of 6 weeks. The CSR presented by the Applicant was a template without content with the exception of tables that listed adverse events. The review and compilation of adverse events are shown in Appendix 9.15. There were 19 adverse events in the NHP-554C arm, 36 adverse events in the IR-ASA arm, and 32 adverse events in the placebo arm. There was no report of SAEs. The number of adverse events in the Gastrointestinal SOC for the NHP-554C, IR-ASA, and placebo arms were 6, 16, and 13, respectively. The severity of the adverse events were restricted to the Gastrointestinal SOC and were reported as mild-to-moderate with the exception of 2 events in the placebo arm (Abdominal Pain and Vomiting) that were recorded as severe. In this study, there was no observable safety signal.

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5.3.15 CLICR 29

CLICR 29 was a multicenter, randomized, double blind parallel group study comparing the safety and efficacy of NHP-554C 325 mg once daily to that of Ticlopidine 250 mg twice daily for 13 months in patients with peripheral vascular disease who have undergone revascularization surgery (France, 1993).

The primary endpoint was "persistence of bypass permeability" assessed by Doppler and clinical examinations performed at predefined intervals. A total of 232 subjects were included in the study: 119 randomized to the NHP-554C arm and 113 randomized to the Ticlopidine arm. Based on the CSR, the study was stopped prematurely by the Sponsor. Only 30 subjects had been in the study long enough to reach the "month 7" visit. ***Table 12*** summarizes the subject exposure in the CLICR 29 trial. A total of 228 subjects completed 1 week of study drug therapy. A total of 214 subjects completed 1 month and 134 subjects completed 4 months. Approximately 13% of the subjects remained in the study by month 7.

Table 12: CLICR 29 Study: Number of Subjects at each study visit

Visit	Number of patients		
	ASACARD group	Ticlopidine group	Total
D8	116	112	228
M1	111	103	214
M4	65	69	134
M7	16	14	30

Source: CLICR 29 CSR, Table 2

Table 13 shows the number of subjects with adverse events in the Gastrointestinal, Blood/Lymphatic, and Skin SOCs retrieved during various visits in the course of the study (Day 8, Month 1, Month 4, and Month 7). Although the number of events is small, the greatest cluster of events was reported at the Month 1 visit in the Gastrointestinal SOC with Ticlopidine having twice the number of adverse events than NHP-554C. A similar proportion of adverse events between the arms were observed when pooling the 3 SOCs.

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Table 13: CLICR 29 Study: Time and SOC Specific Adverse Events

	Number of Subjects with SOC-specific Adverse Events					
Time	GI SOC		Blood SOC		Skin SOC	
	NHP	Ticlopidine	NHP	Ticlopidine	NHP	Ticlopidine
Day 8	7	4	2	1	1	0
Month 1	7	14	2	1	1	3
Month 4	5	9	1	1	0	5
Month 7	0	0	0	1	0	0

Source: CLICR 29 CSR (Tables 3 and 4)

The number of adverse events reported in the CSR is shown in Appendix 9.16. In total, there were 88 adverse events in the NHP-554C arm of which 3 were SAEs, and 89 adverse events in the Ticlopidine arm of which 2 were SAEs. With the exception of the data shown in ***Table 12*** and ***Table 13***, it was not clear when these adverse events took place relative to exposure time.

All the reported SAEs were mortality events. The 3 SAEs in the NHP-554C arm were death consequent to a ruptured thoracic aortic aneurysm, heart failure/metastatic prostate cancer, and myocardial infarction, respectively. The 2 SAEs in the Ticlopidine arm were death consequent to heart failure and neutropenic infection, respectively. The data from this study did not show a safety signal against NHP-554C.

6 Review of Efficacy

Efficacy Summary

Efficacy was not evaluated pursuant to the pre-NDA agreement with the Applicant that an efficacy claim will not be pursued.

7 Review of Safety

Safety Summary

The safety of NHP-554C was evaluated by reviewing 15 clinical trials (1 pivotal and 14 legacy). NHP-554C doses ranged from 20 mg to 1300 mg. The doses of the active comparator, IR-ASA, ranged from 5 mg to 1200 mg. Durations of therapy ranged from a single dose to daily doses of up to 7 months,

Pooled data from the 15 clinical trials showed that 819 subjects were exposed to NHP-554C and 690 subjects were exposed to active comparator (577 subjects on IR-ASA and 113 subjects on Ticlopidine 250 mg bid). A total of 282 subjects (34.4%) on NHP-554C experienced an adverse event, compared to 285 subjects (41.3%) on active

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comparator (IR-ASA and ticlopidine). A total of 10 subjects (1.2%) on NHP-554C, compared to 16 subjects (2.3%) on active comparator, experienced a SAE. There were a total of 5 deaths in the NHP-554C arms (0.6%) and 4 deaths in the active comparator arms (0.6%). A total of 59 subjects (7.2%) on NHP-554C experienced a gastrointestinal adverse event, compared to 79 subjects (11.4%) on active comparator. There were no apparent differences in severity of adverse events between the pooled arms of the trials.

In conclusion, there was no empirical safety signal concerning NHP-554C relative to IR-ASA.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The 15 clinical trials used to evaluate safety are listed in Appendix 9.1. The list of trials were re-arranged to emphasize treatment duration and dose as shown in ***Table 8***. The extent of subject exposure as a function of time for various doses is shown in ***Table 9***.

7.1.2 Categorization of Adverse Events

Adverse events were categorized by System Organ Class in accordance to MedDRA version 16 as depicted in Appendices 9.2 through 9.16.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The adverse event listings were pooled across all 15 trials. Each appendix (9.2 through 9.16) represented the MedDRA based safety data for each of the individual trials, respectively. The Phase 1 pivotal trial (NHP-ASA-01) and the food affect study (ASA-001) were analyzed from the datasets the Applicant provided in the NDA. The remaining trials, all of which were legacy studies conducted in the 1990s for which datasets were not provided, were analyzed from information provided in the respective CSRs.

The pooled adverse events for the NHP-554C arms and the comparator arms of the studies are shown in Appendix 9.17 and Appendix 9.18, respectively. These two appendices referenced the source data listed in appendices 9.2 through 9.16.

7.2 Adequacy of Safety Assessments

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7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Of the 819 subjects exposed to NHP-554C from the 15 studies provided by the Applicant, 482 subjects were healthy volunteers and 337 subjects had a history of atherosclerosis. Twelve of the 15 studies were conducted in healthy volunteers, and 3 studies were conducted on patients with atherosclerosis: U5A-96-02-002 (n=32 on NHP-554C 162.5 mg for 28 days), U5A-98-02-004 (n=186 on NHP-554C 162.5 mg for 6 weeks), and CLICR 29 (n=119 on NHP-554C 325 mg for up to 7 months). Of the 819 subjects, 359 (44%) were exposed to 162.5 mg for various durations ranging from a single dose to up-to 6 weeks, and 287 (35%) were exposed to 325 mg for various durations ranging from a single dose to up-to 7 months.

A majority of the subjects exposed to NHP-554C experienced doses at the level (162.5 mg) or higher than that proposed by the Applicant.

Based on exposure doses, treatment duration, and subject demographics from supportive studies provided by the Applicant, the overall exposure to NHP-554C appeared to be adequate.

The safety assessments in the legacy CSRs were not consistent in many of the CSRs. Descriptions in the content of the CSRs were often not aligned with the listings.

7.2.2 Explorations for Dose Response

Pursuant to agreements between the Division and the Applicant, the dose response exploration focused on the comparison of PK and PD effects between NHP-554C and IR-ASA. Safety evaluations as a function of NHP-554C dose were not performed by the Applicant. From the supportive studies provided by the Applicant, there was sufficient data to explore a possible dose-response safety profile. Adverse events as a function of dose and time for NHP-554C treated subjects are shown in Appendix 9.19. Gastrointestinal adverse events as a function of dose and time for NHP-554C treated subjects are shown in Appendix 9.20. Similarly, adverse events and GI adverse events, each as a function of dose and time, for IR-ASA treated subjects are shown in Appendix 9.21 and Appendix 9.22, respectively. To the extent possible based on the quality of reporting from the legacy CSRs, descriptions of gastrointestinal adverse events were compiled by dose and duration for both NHP-554C and IR-ASA, and are shown in Appendix 2.23.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

Overall safety data is shown in ***Table 14***. There were a total of 282 adverse events in 819 subjects (34.4%) in the NHP-554C arms, and 285 adverse events in 690 subjects (41.3%) in the comparator arms from the 15 trials provided by the Applicant. There were 10 SAEs (5 of these were deaths) in the NHP-554C arms (1.2%) vs. 16 SAEs (4 of these were deaths) in the comparator arms (2.3%).There were 59 adverse events (7.2%) in the HP-554C arms, and 79 adverse events (11.4%) in the comparator arms that were assigned to the Gastrointestinal SOC.

One study (CLICR-29) compared NHP-554C to Ticlopidine. In this study, there were 88 adverse events in 119 atherosclerotic subjects in the NHP-554C 350 mg qd arm, and 89 adverse events in 113 atherosclerotic subjects in the Ticlopidine 250 mg bid arm (see Appendix 9.16). In order to ensure that all comparisons of NHP-554C were made against IR-ASA, the data from CLICR 29 was subtracted from the overall safety data. The results of this sensitivity procedure are shown in the lower half of ***Table 14***. Without the CLICR 29 trial, there were 194 adverse events in 700 subjects (27.7%) in the NHP-554C arms, and 196 adverse events in 577 subjects (34.0%) in the IR-ASA arms from the 14 trials comparing these two aspirin congeners. There were 7 SAEs (2 of these were deaths) in the NHP-554C arms (1.0%) vs. 14 SAEs (2 of these were deaths) in the IR-ASA arms (2.4%). In the Gastrointestinal SOC, there were 35 adverse events (5.0%) in the HP-554C arms, and 48 adverse events (8.3%) in the IR-ASA.

The overall safety data did not suggest a potential safety signal concerning NHP-554C.

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Table 14: Overall Safety Data for NHP-554C

Overall Safety Data		
	NHP-554C (any dose)	Active Comparator (any dose, any time)
Overall Sample Size	819	690
Adverse Events (%)	282 (34.4%)	285 (41.3%)
SAE (%)	10 (1.2%)	16 (2.3%)
Deaths (%)	5 (0.6%)	4 (0.6%)
Gastrointestinal Adverse Events (%)	59 (7.2%)	79 (11.4%)
Overall Safety Data *(Minus CLICR 29 Data due to Ticlopidine as Control Arm)*		
Overall Sample Size	700	577
Adverse Events (%)	194 (27.7%)	196 (34.0%)
SAE (%)	7 (1.0%)	14 (2.4%)
Deaths (%)	2 (0.3%)	2 (0.3%)
Gastrointestinal Adverse Events (%)	35 (5.0%)	48 (8.3%)

Source: Appendices 9.17 and 9.18

7.3.1 Deaths

There were a total of 9 deaths reported in the 15 trials (5 in the NHP-554C arms and 4 in the comparator arms). All the deaths occurred in the 3 trials that evaluated subjects with a history of atherosclerotic disease. Mortality data is shown in Appendix 9.24.

In the U5A-96-02-002 28-day study: NHP-554C 162.5 mg qd .vs. IR-ASA 75 mg qd .vs. IR-ASA 150 mg qd, there was 1 death in each arm:

- NHP-554C arm: 58 year old male who died from an out-of-hospital cardiac arrest 3 weeks post-last dose. There was no reported diagnosis.
- IR-ASA 75 mg arm: 60 year old subject (gender not reported) who died from a subarachnoid hemorrhage 11 days post-last dose.
- IR-ASA 150 mg arm: 76 year old male who died of an acute coronary syndrome 10 days post-last dose.

In the U5A-98-02-004 6-week study: NHP-554C 162.5 mg qd .vs. IR-ASA 150 mg qd, there was 1 death in the NHP-554C arm and no reported deaths in the IR-ASA arm:

- NHP-554C arm: 90 year old male who died from Alzheimer's disease 3 weeks post-start of the study.

In the CLICR 29 study where study drug treatment was variable up to 7 months: NHP-554C 350 mg qd .vs. Ticlopidine 250 mg bid, there were 3 deaths in the NHP-554C arm and 2 deaths in the ticlopidine arm:

- NHP-554C arm:
  - 81 year old male who died from a ruptured thoracic aortic aneurysm 6 weeks post-start of study.
  - 81 year old male who died from either heart failure and/or metastatic prostate cancer 2 weeks post-start of study.
  - 54 year old male who died from myocardial infarction probably related to alcoholism, on the day of randomization. It is not clear if study drug was administered prior to death.
- Ticlopidine arm:
  - 76 year old male who died of a neutropenic pulmonary infection 6 weeks post-start of study.
  - 71 year old male who died of heart failure 6 weeks post-start of study.

Based on the data provided by the Applicant, the mortality data did not demonstrate a safety concern for NHP-554C.

7.3.2 Nonfatal Serious Adverse Events

Table 15 shows the number of SAEs in all the trials that reported SAEs. There were a total of 10 SAEs in the NHP-554C arms of the combined trials, and 16 SAEs in the control arms of the combined trials. All the trials in which there were reported SAEs recruited subjects with a history of atherosclerotic disease. Of the 10 SAEs in the NHP-554C arms, 5 were deaths and 5 were non-fatal SAEs. Of the 16 SAEs in the control arms of the combined trials, 4 were deaths and 12 were non-fatal SAEs. See Section 7.3.1 for a description of the mortality events.

The verbatim terms in the three trials that reported SAEs are found in ***Table 16***. The SAEs were hospitalizations for routine cardiac catheterization; cardiac events (i.e., bradycardia, angina, and myocardial infarction); neurological event (i.e. transient ischemic attack); pulmonary event (i.e. chronic obstructive pulmonary disease); cancer (i.e. myelogenous leukemia); gastrointestinal events (i.e. hematemesis and bright red blood per rectum); and genital-urinary (i.e. circumcision balanitis erotica obliterans). It was not clear why “bright red blood per rectum” was considered an SAE. There was no description of extent of blood loss or any intervention that may have been required. The gastrointestinal SAEs occurred in the IR-ASA arm of study U5A-98-02-004. The distribution of SAEs did not signal a safety concern for NHP-554C.

Table 15: List of Serious Adverse Events

Study	U5A-96-02-002		U5A-98-02-004		CLICR 29		Total	
Appendix Number in Review	9.13		9.14		9.16			
	NHP-554 162.5mg	IR-ASA 75mg and 150mg	NHP-554 162.5mg	IR-ASA 150mg	NHP-554 350mg	Ticlopidine 250mg bid	NHP-554	IR-ASA or ticlopidine
SAE	1	9	6	5	3	2	10	16
Death	1	2	1	0	3	2	5	4
Non-fatal SAE	0	7	5	5	0	0	5	12

Note: all doses are once a day unless otherwise specified

Table 16: Description of non-fatal Serious Adverse Events

Study	U5A-96-02-002		U5A-98-02-004		CLICR 29	
Appendix Number in Review	9.13		9.14		9.16	
	NHP-554 162.5mg	IR-ASA 75mg and 150mg	NHP-554 162.5mg	IR-ASA 150mg	NHP-554 350mg	Ticlopidine 250mg bid
SAE Description	----------	COPD Routine cardiac cath TIA Routine cardiac cath Bradycardia Routine cardiac cath Myelogenous leukemia	TIA MI Routine cardiac cath Breast cancer Syncope	MI Hematemesis Angina Bright red blood per rectum Balanitis	-----	----------

COPD: Chronic Obstructive Pulmonary Disease; TIA: Transient Ischemic Attack; MI: Myocardial Infarction

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7.3.3 Adverse Events

Appendix 9.17 (Adverse Event compilation for NHP-554C exposed subjects) and Appendix 9.18 (Adverse Event compilation for IR-ASA exposed subjects) show a broad spectrum distribution of adverse events amongst the SOCs. Pursuant to the clinical review strategy, particular attention was given to the GI system in order to determine the existence of any safety issues as a consequence of continued ASA release downstream in the GI tract. As the two appendices indicate and as summarized in ***Table 14***, there were 59 Gastrointestinal adverse events in the NHP-554 arms of the 15 clinical studies (57 classified as GI and 2 classified as Hepatobiliary that were lumped into the Gastrointestinal SOC) and 79 Gastrointestinal adverse events in the comparator arms of the 15 studies (77 classified as GI and 2 classified as Hepatobiliary that were lumped into the Gastrointestinal SOC).

Gastrointestinal adverse events (see Appendix 9.23) were described as eructation, abdominal discomfort, abdominal pain, anorexia, epigastric pain, loose stools, dyspepsia, nausea, vomiting, diarrhea, constipation, flatulence, reflux, gastric ulcer, hepatobiliary, and blood per rectum. All of these events were considered not serious except for “bright red blood per rectum” in the NHP-554C arm of study U5A-98-02-004. The description of that SAE was not provided (e.g. extent of blood loss, transfusion requirement, source of bleed {hemorrhoids, polyp, fissure, etc.}). The adverse events classified as Hepatobiliary in study U5A-97-02-003, 2 in the NHP-554C arm and 2 in the IR-ASA arm, were not described in that study’s CSR, but were listed in that CSR’s Table 25 (treatment emergent signs and symptoms) as “hepatic function abnormal” using World Health Organization (WHO) preferred terms. The two adverse events described as “gastric ulcer” found in the IR-ASA arm of study U5A-98-02-004 were considered mild.

The description of gastrointestinal adverse events did not precipitate a safety concern regarding NHP-554C.

7.3.4 Dropouts and/or Discontinuations

Evaluation of drop-outs focused on 4 trials: U5A-98-02-004, U5A-96-02-002, CLICR 29, and NHP-ASP-01. The reason for this selection of studies to evaluate withdrawals was based on the following:

- Compared to the other legacy studies, the two “U5A” studies and the CLICR 29 studies involved the target patient population and had substantially larger sample sizes. The doses in these trials were the target dose proposed by the Applicant and the duration of treatment was at least 1 month. An evaluation of withdrawal in this subset of studies was considered to potentially provide some insight about drug tolerability in a target patient population.
- NHP-ASP-01 was the pivotal trial serving as the basis of this NDA and was the only study conducted in recent times.

Data on withdrawals from the U5A-98-02-002, U5A-98-004, and CLICR 29 studies are shown in Appendix 9.25, Appendix 9.26, and Appendix 9.27, respectively.

In study U5A-96-02-002, there were a total of 11 withdrawals in the sample size of 98. Three withdrawals occurred in the pre-treatment phase, all due to protocol violations. Three withdrawals occurred in the NHP-554C 162.5 mg arm, all due to adverse events. There was one withdrawal in the EC-IR-ASA 75 mg arm due to an adverse event. In the EC-IR-ASA 150 mg arm, there were 4 withdrawals (1 due to adverse event, 3 due to protocol violations). The adverse events leading to withdrawal in the U5A-96-02-002 study were described as indigestion, nausea/dyspnea/dizziness in the NHP-554C arm, stomach pain and loin pain in the two EC-IR-ASA arms respectively.

In the U5A-98-004 study, there were 50 withdrawals (n=186) from the NHP-554C 162.5 mg arm and 52 withdrawals (n=196) from the EC-IR-ASA 150 mg arm. The reasons for withdrawal from the NHP-554C arm were adverse events (27), protocol violations (14), non-compliance (6), death (1), and lost-to-follow up (2). The death in this case was the 90 year old male who died from Alzheimer's disease 3 weeks post-start of the study. The reasons for withdrawal from the EC-IR-ASA arm were adverse events (21), protocol violations (13), non-compliance (15), and "failure to return" (3). The adverse events leading to withdrawal in the U5A-98-02-004 study were not described sufficiently for an accurate accounting. That study's CSR-Table 11 specified 11 withdrawals due to GI adverse events based on subject diaries. The remainder of the withdrawals for adverse events was not described.

In the CLICR 29 study, there were 30 withdrawals (n=119) from the NHP-554C 350 mg qd arm and 23 withdrawals (n=113) from the ticlopidine 250 mg bid arm. The reasons for withdrawal from the NHP-554C arm were adverse events (16), protocol violations (3), "Reason unspecified" (10) and "lack of efficacy" (1). The reasons for withdrawal from the ticlopidine arm were adverse events (13), protocol violations (2). "Reason unspecified" (5), and "lack of efficacy" (3). The adverse events leading to withdrawal in this study were not described.

A summary of withdrawals from the three legacy trials evaluating subjects with atherosclerosis is shown in ***Table 17***.

Table 17: Withdrawals from legacy trials evaluating subjects with atherosclerosis

Withdrawals in trials of Subjects with Atherosclerosis				
	NHP-554C (any dose) (Number of Withdrawals) /Sample Size (%)	Withdrawal Due to Adverse Events / Total Withdrawals (%)	IR-ASA (any dose) or ticlopidine in CLICR 29 (Number of Withdrawals) /Sample Size	% Withdrawal Due to Adverse Events
U5A-96-02-002	3/32 (9%)	3/3 (100%)	5/66 (8%)	2/5 (40%)
U5A-98-02-004	50/186 (27%)	28/50 (56%)*	52/196 (27%)	21/52 (40%)
CLICR 29**	30/119 (25%)	16/30 (53%)	23/113 (20%)	13/23 (57%)
Total	83/337 (25%)	47/83 (57%)	80/375 (21%)	36/80 (45%)

Source: Appendix 9.25, Appendix 9.26, and Appendix 9.27
** A death in this study, listed separately in Appendix 9.26, was lumped as an adverse event resulting in withdrawal.*
*** CLICR 29 compared NHP-554C to ticlopidine*

The overall rates of withdrawals due to an adverse event were similar between the NHP-554C and comparator arms. The rate of withdrawal due to adverse events was higher in the NHP arm compared to the IR-ASA arm in the U5A-98-02-004 study, but slightly lower in the NHP-554C arm compared to ticlopidine in the CLICR-29 study. The quality of safety data collection could not be ascertained in these decades-old legacy studies. There was no observable trend in withdrawals consequent to adverse events that may establish a safety signal for NHP-554C.

In the NHP-ASP-01 pivotal PK/PD trial, there were 3 withdrawals. One of was due to an adverse event. The 3 withdrawals are described herewith:

- Subject 001011: withdrew due to an adverse event (see section 7.3.5 of this review)
- Subject 001012: completed Period 1 (IR-ASA 20 mg) was withdrawn due to a protocol violation (tested positive for barbiturates).
- Subject 001033: completed Period 1 (NHP-554C 81 mg) but was withdrawn due to a protocol violation (tested positive for amphetamines).

7.3.5 Significant Adverse Events

There was one reported adverse event from study NHP-ASP-01 that was thought to merit a detailed review.

Subject 001011: 49 year old healthy Hispanic female with no reported past medical history or relevant prior medications, sustained an increase in liver enzymes (ALT, AST, GGT) from a normal baseline. The details of the liver function tests are shown in ***Table 18***.

Table 18: NHP-ASP-01 Possible Drug-Induced Liver Function Adverse Event

Visit NHP-ASP-01 Subject 001011	Liver Function Test				
	ALT (U/L)	AST (U/L)	GGT (IU/L)	Alkaline Phosphatase (U/L)	Bilirubin (umol/L)
Screening	15	19	31	102	10.26
Period 1 Day -1 pre-dose	16	19	34	101	8.55
Period 1 Day 1 Dosing IR-ASA 20mg	---	---	---	---	---
Period 1 Day 2 post-dose	15	18	34	103	8.55
Washout					
Period 2 Day -1 pre-dose	13	18	24	93	8.55
Period 2 Day 1 Dosing NHP-544C 20 mg	---	---	---	---	---
Period 2 Day 2 post-dose	422	639	351	165	20.52
Repeat Assessment Day 4	161	56	208	133	---
Repeat Assessment Day 13	25	19	108	104	---
Repeat Assessment Day 19	---	---	82	---	---
Early Termination Day 20	18	21	84	104	11.97

Normal Ranges: ALT 10-60 U/L, AST 14-47 U/L GGT 6-74 IU/L, Alkaline Phosphatase 41-129 U/L, Bilirubin 5.13-27.37 umol/L. Source of Table 16: NHP-ASP-01 Data Listing 16.2.8.6.2

The subject received IR-ASA 20 mg during Period 1 and did not experience an adverse event. After the 2 week per protocol washout, the subject entered Period 2 where she was dosed with NHP-554C 20 mg (Day 1). On Day 2 of Period 2, the ALT level rose to 7 x upper limit of normal (ULN). The AST level rose to 14x ULN. The GGT level rose to 5x ULN. Alkaline Phosphatase rose to 1.3x ULN. Bilirubin rose from 10.26 (umol/L) to 20.52 (umol/L) but remained within normal limits. ALT, AST, Alkaline Phosphatase returned to normal approximately 2 weeks post dose. Bilirubin levels were always within normal limits but decreased to the approximate level of the subject's baseline 2 weeks post-dose. GGT decreased but remained elevated from baseline (i.e. 84 IU/L). Tests for hepatitis B, C and antinuclear antibodies were negative. The subject denied use of alcohol, medications, or other drugs prior to admission or while in the clinical unit. The patient discontinued from the study. The subject did not respond to repeated requests for follow-up. She was therefore considered lost-to-follow up where her increased GGT was considered not resolved.

Hy's Law cases have three components (Guidance for the Industry, Drug Safety, 2009):

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the non-hepatotoxic control drug or placebo.
- Among trial subjects with ALT or AST elevations, often much greater than 3xULN, one or more also show elevation of serum total bilirubin to > 2xULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).
- No other reason can be found to explain increased levels in the combination of ALT or AST and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

Based on the Guidance to Industry document, finding one Hy's Law case in the clinical database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe Drug-Induced Liver Injury (DILI) when given to a larger population.

This case did not satisfy the criteria for Hy's Law because the subject's bilirubin (presumed total bilirubin) level remained within normal limits despite doubling at peak from the subject's baseline. Although I assessed this adverse event as probably drug-related, there were no other similar events at higher doses of NHP-554C. Also, there was no evidence of DILI in the legacy trials, especially those in which NHP-554C was administered at higher doses for extended periods of time (i.e. 1→ 7 months). Therefore, this single case of transient liver transaminase elevation is not likely to be predictive of NHP-554C-mediated DILI.

7.3.6 Submission Specific Primary Safety Concerns

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7.4 Supportive Safety Results

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A dose dependency exploration was conducted to the extent possible from the data provided in the 14 legacy CSRs and the NHP-ASP-01 pivotal trial. Adverse events for NHP-554C treated subjects as a function of dose and time are shown in Appendix 9.19 for all events and Appendix 9.20 for gastrointestinal events. Similarly, adverse events for IR-ASA treated subjects as a function of dose and time are shown in Appendix 9.21for all events and Appendix 9.22 for gastrointestinal events. The number of adverse events divided by the sample size in each of those studies per dose was specified in the time slot window representing the duration of treatment in those respective studies.

The evaluation of dose-dependency for adverse events was impacted by the following ascertainment liabilities:

- The data was compiled from different legacy trials with variability in design characteristics and sample sizes.
- The majority of the subjects in all the trials received either 162.5 mg or 325 mg NHP-554C (646/819—see ***Table 9***). The sample size in the remaining doses was too small for an adequate dose dependency-safety analysis.
- The highest dose (1300 mg) was administered for 5 days to 22 healthy subjects in study CLFT 103-9802. There were 19 reported adverse events without specifying what study drug the subjects were taking when the adverse events occurred. Therefore, the adverse events were attributed to NHP-554C 1300mg thereby artificially impacting the dose-dependency adverse event relationship.
- The dose-dependency review was impacted by the time variability inherent with each dose.
- A majority of the subjects taking NHP-554C 162.5 mg or 325 mg were patients with atherosclerotic disease (337/646) administered study drug for prolonged periods of time whereas the subjects taking other doses (both lower and higher doses) were healthy subjects (see ***Table 8***).
- The determination of drug causality was not evaluable.

These ascertainment liabilities attenuated the quality of an exploratory dose-dependency relationship for adverse events. The data from the relevant appendices referenced in this section are graphically illustrated in ***Figure 6***. The data was represented as percent of adverse events (number of adverse events/sample size) as a

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time-independent function of dose. The spike in the NHP-554C adverse event profile for the 1300 mg dose represented the data from the CLFT 103-9802 trial where 19 reported adverse events occurred in the 22 subjects without reference to the study drug taken at the time of the adverse events. Consequently, these adverse events were attributed to NHP-554C 1300 mg. The spike in the NHP-554C adverse event profile for the 325 mg dose was based on combined data from NHP-ASP-01 (5 adverse events/20 subjects single dose), ASA-001 (11 adverse events/ 50 subjects single dose), PKCR-0491 (0 adverse events/12 subjects single dose), PKFT-97-101 (1 adverse event/24 subjects dosing < 1 week), ASA-002 (12 adverse events/25 subjects dosing 1-2 weeks), U5A-96-02-001 (14 adverse events/24 subjects 3 weeks dosing), CLICR 28 (1 adverse event/13 subjects 4 weeks dosing), and CLICR 29 (88 adverse events/119 subjects up to 7 months dosing): 132 adverse events/287 subjects (46%). The data for this dose was driven by the CLICR 29 study that evaluated NHP-554C in patients with peripheral vascular disease for variable time-periods up to 7 months.

The spike in IR-ASA adverse event profile for the 75 mg dose represented the data from the U5A-96-02-002 where there were 29 reported adverse events in 34 subjects (85%) following 4 weeks of dosing. The spike in the IR-ASA adverse event profile for the 150 mg dose was based on combined data from U5A-96-02-002 (14 adverse events/32 subjects 4 weeks dosing), U5A-98-02-004 (72 adverse events/196 subjects 6 weeks dosing), and U5A-97-02-003 (36 adverse events/40 subjects 6 weeks dosing): 122 combined adverse events/268 subjects (46%). The spike in the IR-ASA event profile for the 500 mg dose was based on a single dose study (CLFT-102-90-01) where 14 adverse events were reported in 24 healthy subjects (58%) single dose. In one study (CLICR 28), where IR-ASA 350 mg was evaluated in 13 healthy volunteers for 4 weeks, there was not a single adverse event.

The ascertainment liabilities inherent in a heterogeneous database provided in legacy CSRs, in concert with arbitrary attribution due to CSR non-specificity, rendered a dose dependency relationship for adverse events inconclusive.

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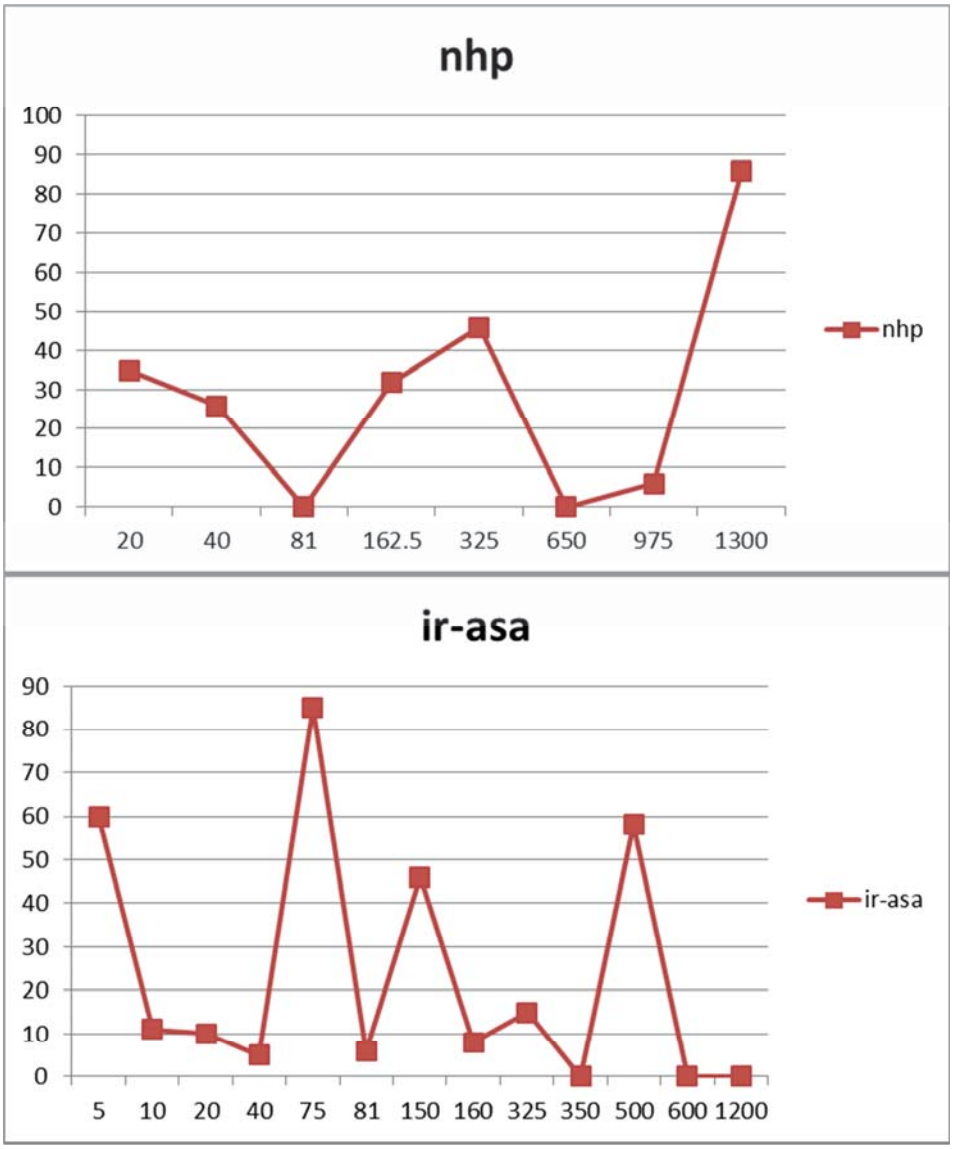
Figure 6: Dose Dependency for Adverse Events (Percent: AE/#Subjects vs Dose)



Source: Appendix 9.19 and Appendix 9.21

7.5.2 Time Dependency for Adverse Events

A time dependency exploration was conducted to the extent possible from the legacy CSRs and the NHP-ASP-01 trial. As described in section 7.5.1 of this review, adverse events for NHP-554C treated subjects as a function of dose and time are shown in Appendix 9.19 for all events and Appendix 9.20 for gastrointestinal events. Similarly, adverse events for IR-ASA treated subjects as a function of dose and time are shown in Appendix 9.21 for all events and Appendix 9.22 for gastrointestinal events. The

evaluation of the time-dependency for adverse events was impacted by the following ascertainment liabilities:

- As described in section 7.5.1, the data was compiled from different legacy trials with variability in design characteristics and sample sizes.
- In the trial with the longest exposure period (CLICR 29), patients were administered NHP-554C 325 mg or Ticlopidine 250 mg b.i.d. for variable time periods up to 7 months. With the exception of 3 SOCs (i.e. Gastrointestinal, Hemostasis, Cutaneous), the CSR was not entirely clear about the duration of therapy at the time of the adverse events in this study.
- The largest time-dependent sample sizes occurred in trials with the longest duration of therapy (i.e. 223 subjects taking NHP-554C 162.5 mg for 6 weeks; 119 subjects taking NHP-554C for variable time periods up to 7 months in the prematurely terminated study CLICR 29—see ***Table 9***). The majority of subjects in these trials were patients with atherosclerotic disease presenting with peripheral vascular disease. Sample sizes in trials with shorter time durations were considerably smaller, and the subjects in these trials were healthy volunteers.
- The time-dependency review was impacted by a lack of subjects for multiple time periods for the majority of the doses (other than 162.5 mg and 325 mg), thereby leaving multiple gaps in each timeframe.
- The determination of drug causality was not evaluable.

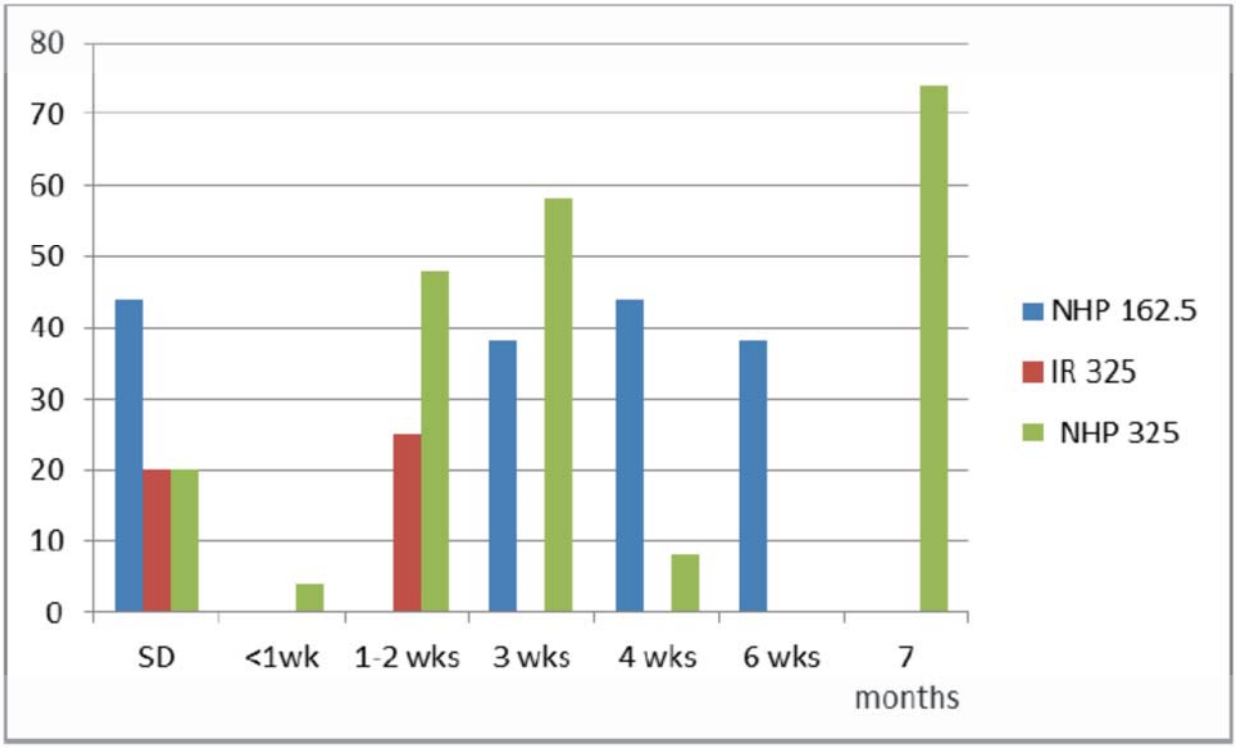
These ascertainment liabilities attenuated the quality of an exploratory time-dependency relationship for adverse events. Two doses of NHP-554C (162.5 mg, and 325 mg) had exposure data for every time window delineated in the referenced appendices. Only 1 dose of IR-ASA (325 mg) had exposure data for multiple time windows. The time-dependency data for the two NHP-554C doses and the IR-ASA dose from the referenced appendices are graphically illustrated in ***Figure 7***. The data was represented as percent of adverse events (number of adverse events/sample size) as a function of time for the doses explored.

There appeared to be a general time-dependency for adverse events with the NHP-554C 325 mg dose. At this dose, the single dose data was derived from 3 studies: NHP-ASP-01 (5 adverse events/20 subjects), ASA-001 (11 adverse events/50 subjects) and PKCR-0491 (0 adverse events/12 subjects): 16 adverse events/82 subjects (20%). The data under the timeslot (< 1 week) came from the PKFT-97-101 study (1 adverse event/24 subjects): 4%. The data for 1-2 weeks exposure period was derived from the ASA-002 study (12 adverse events/25 subjects): 48%. The 3 week exposure data came from the U5A-96-02-001 study (14 adverse events/24 subjects): 58%. The 4 week exposure data came from CLICR 28 (1 adverse event/13 subjects): 8%. Finally, the data for the up-to-7 months' timeframe came from the CLICR 29 trial (88 adverse events/119 subjects): 74%. The distribution of adverse events in this trial clustered around Cardiac, GI, General, Infection, Nervous System, and Respiratory. This

distribution, over a 7 month period of time, was within that normally expected for patients with peripheral vascular -atherosclerotic disease.

The adverse event data for the NHP-554C 325 mg dose was impacted by small sample sizes (e.g. 12 adverse events/25 subjects, 14 adverse events/24 subjects) in the time periods between the single dose and the 7 month scale. This, in addition to other ascertainment liabilities (i.e. heterogeneous subject population), rendered a time-dependency exploration for adverse events inconclusive. These same issues were in effect for the NHP-162.5 mg and IR-ASA 325 mg doses.

Figure 7: Time Dependency for Adverse Events (Percent: AE/#Subjects vs Time)



Source: Appendix 9.19 and Appendix 9.21

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

Not applicable

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

Not applicable

9 Appendices

9.1 Study Listings ranked by NHP-554C Dose and Duration of Treatment

Study #	Location (year)	Study Design	Dose (mg)	Sample Size	Age Range (mean)years
NHP-ASP-01	USA (2103)	PK/PD: Single dose open-label 4-way cross over	NHP: 20, 40, 81, 162.5, or 325. IR: 5. 10, 20, 40, or 81	NHP: 50 IR: 50	19-55 (36.9)
ASA-001	USA (1997)	PK/PD: Single dose open label 3-way cross over	NHP: 325 IR: 325	26 healthy volunteers	19-39 (28)
PKCR-0491	France (1992)	PK/PD: Single dose randomized open label 3-way cross over	NHP: 325 IR: 350	12 healthy males	20-32 (24)
ASA-002	USA (1997)	PK/PD: Multiple dose randomized open label cross over	NHP: 325 qd x 7 days ASA delayed-release: 325 qd x 7 days	25 healthy volunteers	19-38 (27)
CLICR 28	France (1992-1993)	PK/PD: Multiple dose randomized open label, cross over	NHP: 325 qd x 28 days IR: 350 qd x 28 days	13 healthy volunteers	20-29 (23)
CLICR 30	France (1994)	PK/PD: Multiple dose randomized open label cross over	NHP: 162.5 qd x 10 days IR: 160 qd x 10 days	12 healthy volunteers	21-36 (25)
CLFT-103-9802	UK (1999-2000)	GI toxicity and tolerability: 6 week single site randomized double-blind	NHP: 650 qd x 5 days NHP: 1300 qd x 5 days IR: 600 qd x 5 days	23 healthy volunteers (9 males, 14 females)	19-45 (27)

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		double-dummy, 4-way cross over	IR: 1200 qd x 5 days		
U5A-97-02-003	UK (1997-1998)	GI toxicity and tolerability: 6 week single site, randomized double-blind, double-dummy, parallel group	NHP: 162.5 qd x 6 weeks IR: 150 qd x 6 weeks Placebo: qd x 6 weeks	114 healthy volunteers: NHP: 37 (18 males, 19 females) IR: 40 (23 males, 17 females) Placebo: 37 (17 males, 20 females)	18-50 (mean not reported)
U5A-96-02-001	UK (1996-1997)	GI toxicity and tolerability: 6 week single site, randomized double-blind, cross over	Low Dose Regimen NHP: 162.5 qd x 21 days Enteric-coated IR: 75 qd x 21 days High Dose Regimen NHP: 325 qd x 21 days Enteric-coated IR: 325 qd x 21 days	48 healthy volunteers: 24 high dose (19 males, 5 females); 24 low dose (14 males, 10 females)	19-43 (mean not reported)
CLFT 102-9001	Germany (2000)	Analgesic effect: 6 week, single site, randomize double-blind, double-dummy, 4-way cross over	NHP: 975 qd x 6 weeks IR: 500 qd x 6 weeks Naproxen: 220 or placebo qd x 6 weeks	24 healthy volunteers (14 males. 10 females)	19-46 (27)
PKFT 97101	France (1997)	PK/PD: Dosing requirement for NHP (load + maintenance): 9 week randomized open label 2	Between each 5 day treatment cycle: 14 day washout period: NHP: 325 qd	24 healthy volunteers/arm	19-36 (26)

		arm study	x 5 days→650 qd x 1 day→325 qd x 4 days→975 qd x 1 day→325 qd x 4 days IR: 325 qd x 5 days for each cycle		
CLICR 29*	France (1993)	Atherosclerosis efficacy and safety study: 13 month, multicenter, randomized double blind parallel group	NHP: 325 qd x 13 months Ticlopidine: 250 bid x 13 months	Total: 232 (197 males, 34 females) subjects with arteriosclerosis obliterans (stage II-IV) requiring vascular surgery. NHP: 119 (99 males, 20 females) Ticlopidine: 113 (98 males, 14 females)	36-91 (65)
U5A-96-02-002*	UK (1996-1997)	Atherosclerosis efficacy and safety study: 1 month, single-blind, randomized parallel group	Enteric-coated (EC) IR 75 qd x 14 days→NHP 162.5 or EC-IR 75 qd x 28 days	Total: 95 with arteriosclerotic disease (angina, bypass grafts). NHP: 34 (26 males, 8 females) EC-IR 150 mg: 36 (29 males, 7 females) EC-IR 75 mg: 34 (27 males, 7 females)	37-83 (62)
U5A-98-02-004*	UK (1999-2000)	Atherosclerosis Tolerability	Placebo qd x 2 weeks→	380 with atherosclerosis.	36-91 (65)

		study: 6 week single site randomized double-blind parallel group	NHP 162.5 qd or IR 150 qd x 6 weeks	NHP: 186 (112 males, 72 females: *does not add up*) IR: 196 (113 males, 83 females)	
PKFT 9542	France (1996)	PK: open randomized 2-way cross over single dose	NHP (FT03 vs. FT02 formulations): 162.5 single dose with each formulation with 2-week washout between doses	FT03: 25 FT02: 25 All Males	19-33 (25)

Source of Data: Module 2.5 Clinical Overview.
** Patients with atherosclerotic disease*

9.2 Safety Data from Study NHP-ASP-01

Drug Treatment Single Dose	NHP-554C					IR-ASA				
Dose (mg)	20	40	81	162.5	325	5	10	20	40	81
Sample Size	20	19	18	18	20	20	19	20	20	18
Adverse Events (AE)	7	5	0	8	5	12	2	2	1	1
Severity of AE										
-mild	3	5	--	7	4	11	2	2	1	1
-moderate	4	--	--	1	1	1	--	--	--	--
-severe										
SAE	--	--	--	--	--	--	--	--	--	--
Death										
MedDRA SOC										
Blood and Lymphatic										
Cardiac										
Congenital										
Ear and Labyrinth										
Endocrine										
Eye										
GI	1	2		2		3				
General & Admin site		2		2		1		2	1	
Hepatobiliary										
Immune System										
Infection/Infestation										
Injury/Poison/Procedures				1						
Investigations	4					1				
Metabolism & Nutrition						1				
Musculoskeletal & Connective Tissue							2			
Neoplasms										
Nervous System	2	1		1	2	3				1
Pregnancy/Perinatal										
Psychiatric						2				
Renal/Urinary										
Reproductive/Breast										
Respiratory/Thoracic/Mediastinal				2	3	1				
Skin/subcutaneous										
Surgical/medical procedures										
Vascular disorders										

Reference ID: 3744664

9.3 Safety Data from Study PKFT 9542

No Clinical Adverse Events were reported

APPEARS THIS WAY ON ORIGINAL

9.4 Safety Data from Study ASA-001

Drug Treatment Single Dose	**NHP-554C 325 mg Fasted State**	**NHP-554C 325 mg Fed State**	**IR-ASA 325 mg Fed State**
Sample Size	26	24	25
Adverse Events (AE)	6	5	5
Severity of AE			
-mild	4	4	4
-moderate	2	1	1
-severe			
SAE	0	0	0
Death	0	0	0
MedDRA SOC			
Blood and Lymphatic			1
Cardiac			
Congenital			
Ear and Labyrinth	1		
Endocrine			
Eye			
GI		1	1
General & Admin site	4	3	3
Hepatobiliary			
Immune System			
Infection/Infestation			
Injury/Poison/Procedures			
Investigations			
Metabolism & Nutrition	1		
Musculoskeletal & Connective Tissue			
Neoplasms			
Nervous System			
Pregnancy/Perinatal			
Psychiatric			
Renal/Urinary			
Reproductive/Breast			
Respiratory/Thoracic/Mediastinal			
Skin/subcutaneous			
Surgical/medical procedures			
Vascular disorders		1	

Reference ID: 3744664

9.5 Safety Data from Study PKCR 0491

No Adverse Events were reported.

APPEARS THIS WAY ON ORIGINAL

9.6 Safety Data from Study PKFT 97101

Drug Treatment Single Dose, Maintenance Dose	**NHP-554-C 325 mg d1→d5**	**NHP-554-C 650 mg d1→325 mg d2-d5**	**NHP-554-C 975 mg d1→325 mg d2-d5**	**IR-ASA 325 mg d1→d5**
Sample Size	24	24	24	24
Adverse Events (AE)	1	0	0	0
Severity of AE	Not reported			
-mild				
-moderate				
-severe				
SAE				
Death				
MedDRA SOC				
Blood and Lymphatic				
Cardiac				
Congenital				
Ear and Labyrinth				
Endocrine				
Eye				
GI				
General & Admin site				
Hepatobiliary				
Immune System				
Infection/Infestation	1			
Injury/Poison/Procedures				
Investigations				
Metabolism & Nutrition				
Musculoskeletal & Connective Tissue				
Neoplasms				
Nervous System				
Pregnancy/Perinatal				
Psychiatric				
Renal/Urinary				
Reproductive/Breast				
Respiratory/Thoracic/Mediastinal				
Skin/subcutaneous				
Surgical/medical procedures				
Vascular disorders				

Reference ID: 3744664

9.7 Safety Data from Study CLFT 102-9001

Drug Treatment Single Dose	**PLACEBO**	**NHP-554C 975 mg**	**IR-ASA 500 mg**	**NAPROXEN 200 mg**
Sample Size	24	24	24	24
Adverse Events (AE)	4	3	14	6
Severity of AE	Not reported	Not reported	Not reported	Not reported
-mild				
-moderate				
-severe				
SAE				
Death				
MedDRA SOC				
Blood and Lymphatic		1	1	
Cardiac				
Congenital				
Ear and Labyrinth			1	1
Endocrine				
Eye				
GI	1		6	2
General & Admin site			2	2
Hepatobiliary				
Immune System				
Infection/Infestation		1	1	
Injury/Poison/Procedures				
Investigations				
Metabolism & Nutrition				
Musculoskeletal & Connective Tissue				
Neoplasms				
Nervous System	3	1	3	1
Pregnancy/Perinatal				
Psychiatric				
Renal/Urinary				
Reproductive/Breast				
Respiratory/Thoracic/Mediastinal				
Skin/subcutaneous				
Surgical/medical procedures				
Vascular disorders				

Reference ID: 3744664

9.8 Safety Data from Study CLFT 103-9802

Drug Treatment 5-Days	**IR-ASA 600 mg**	**NHP-554C 650 mg**	**IR-ASA 1200 mg**	**NHP-554C 1300mg**
Sample Size	22	22	22	22
Adverse Events (AE)	---	---	---	19
Severity of AE				Not reported
-mild				
-moderate				
-severe				
SAE				
Death				
MedDRA SOC				
Blood and Lymphatic				
Cardiac				
Congenital				
Ear and Labyrinth				
Endocrine				
Eye				
GI				7
General & Admin site				1
Hepatobiliary				
Immune System				
Infection/Infestation				
Injury/Poison/Procedures				
Investigations				
Metabolism & Nutrition				
Musculoskeletal & Connective Tissue				
Neoplasms				
Nervous System				4
Pregnancy/Perinatal				
Psychiatric				
Renal/Urinary				1
Reproductive/Breast				1
Respiratory/Thoracic/Mediastinal				5
Skin/subcutaneous				
Surgical/medical procedures				
Vascular disorders				

Reference ID: 3744664

9.9 Safety Data from Study ASA-002

Drug Treatment 7-Days	**NHP-554C 325 mg**	**Ecotrin® 325 mg**		
Sample Size	25	24		
Adverse Events (AE)	12	6		
Severity of AE				
-mild	12	6		
-moderate				
-severe				
SAE				
Death				
MedDRA SOC				
Blood and Lymphatic				
Cardiac		1		
Congenital				
Ear and Labyrinth				
Endocrine				
Eye				
GI		1		
General & Admin site	7	0		
Hepatobiliary				
Immune System				
Infection/Infestation				
Injury/Poison/Procedures				
Investigations				
Metabolism & Nutrition				
Musculoskeletal & Connective Tissue				
Neoplasms				
Nervous System				
Pregnancy/Perinatal				
Psychiatric				
Renal/Urinary				
Reproductive/Breast				
Respiratory/Thoracic/Mediastinal	5	4		
Skin/subcutaneous				
Surgical/medical procedures				
Vascular disorders				

Reference ID: 3744664

9.10 Safety Data from Study CLICR 30

Drug Treatment 10-Days	**NHP-554C 162.5 mg**	**IR-ASA 160 mg**		
Sample Size	12	12		
Adverse Events (AE)	0	1		
Severity of AE		Not reported		
-mild				
-moderate				
-severe				
SAE				
Death				
MedDRA SOC				
Blood and Lymphatic				
Cardiac				
Congenital				
Ear and Labyrinth				
Endocrine				
Eye				
GI				
General & Admin site				
Hepatobiliary				
Immune System				
Infection/Infestation				
Injury/Poison/Procedures				
Investigations				
Metabolism & Nutrition				
Musculoskeletal & Connective Tissue				
Neoplasms				
Nervous System				
Pregnancy/Perinatal				
Psychiatric				
Renal/Urinary				
Reproductive/Breast				
Respiratory/Thoracic/Mediastinal				
Skin/subcutaneous				
Surgical/medical procedures		1		
Vascular disorders				

Reference ID: 3744664

9.11 Safety Data from Study U5A-96-02-001

Drug Treatment 21-Days	**NHP-554C 162.5 mg**	**NHP-554C 325 mg**		
Sample Size	24	24		
Adverse Events (AE)	9	14		
Severity of AE				
-mild	8	14		
-moderate	1			
-severe				
SAE	0	0		
Death	0	0		
MedDRA SOC				
Blood and Lymphatic				
Cardiac				
Congenital				
Ear and Labyrinth				
Endocrine				
Eye				
GI	4	3		
General & Admin site				
Hepatobiliary				
Immune System				
Infection/Infestation	1			
Injury/Poison/Procedures	1			
Investigations				
Metabolism & Nutrition				
Musculoskeletal & Connective Tissue				
Neoplasms				
Nervous System		5		
Pregnancy/Perinatal				
Psychiatric				
Renal/Urinary		1		
Reproductive/Breast				
Respiratory/Thoracic/Mediastinal	3	4		
Skin/subcutaneous				
Surgical/medical procedures				
Vascular disorders		1		

Reference ID: 3744664

9.12 Safety Data from Study CLICR 28

Drug Treatment 28-Days	**NHP-554C 325 mg**	**IR-ASA 350 mg**		
Sample Size	13	13		
Adverse Events (AE)	1	0		
Severity of AE	Not reported			
-mild				
-moderate				
-severe				
SAE				
Death				
MedDRA SOC				
Blood and Lymphatic				
Cardiac				
Congenital				
Ear and Labyrinth				
Endocrine				
Eye				
GI				
General & Admin site				
Hepatobiliary				
Immune System				
Infection/Infestation				
Injury/Poison/Procedures	1			
Investigations				
Metabolism & Nutrition				
Musculoskeletal & Connective Tissue				
Neoplasms				
Nervous System				
Pregnancy/Perinatal				
Psychiatric				
Renal/Urinary				
Reproductive/Breast				
Respiratory/Thoracic/Mediastinal				
Skin/subcutaneous				
Surgical/medical procedures				
Vascular disorders				

Reference ID: 3744664

9.13 Safety Data from Study U5A-96-02-002

Drug Treatment 28-days	**NHP-554C 162.5 mg**	**IR-ASA 150 mg**	**IR-ASA 75 mg**
Sample Size	32	32	34
Adverse Events (AE)	14	14	29
Severity of AE	Not reported	Not reported	Not reported
-mild			
-moderate			
-severe			
SAE	1	3	6
Death	1*	1*	1*
MedDRA SOC			
Blood and Lymphatic			
Cardiac	1		1*
Congenital			
Ear and Labyrinth			1
Endocrine			
Eye	1		
GI	4	1	5
General & Admin site			
Hepatobiliary			
Immune System			
Infection/Infestation	1	2	2
Injury/Poison/Procedures			
Investigations			
Metabolism & Nutrition			1
Musculoskeletal & Connective Tissue			2
Neoplasms		1*	
Nervous System	2	1	1*
Pregnancy/Perinatal			
Psychiatric			1
Renal/Urinary			1
Reproductive/Breast			
Respiratory/Thoracic/Mediastinal		3	3#
Skin/subcutaneous	2		
Surgical/medical procedures	1	2***	4****
Vascular disorders	1	1	1

**SAE. Also note that SAEs were listed separately from AEs in the CSR. This table combines them so that the number of adverse events includes those that were also considered SAEs.*
*** 1 of the 2 was a SAE (i.e. hospitalization for TIA); *** 1 of the 2 was a SAE (hospitalization for a procedure); **** 2 of the 4 were SAEs (hospitalization for routine cardiac angiographically x 2)*
 # 1 of the 3 was a SAE (exacerbation of COPD)

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9.14 Safety Data from Study U5A-98-02-004

Drug Treatment 6 Weeks	**NHP-554C 162.5 mg**	**IR-ASA 150 mg**		
Sample Size	186	196		
Adverse Events (AE)	66	72		
Severity of AE				
-mild	3*	6*		
-moderate		6*		
-severe		1*		
SAE	6	5		
Death	1	0		
MedDRA SOC				
Blood and Lymphatic	0	1		
Cardiac	5**	4**		
Congenital				
Ear and Labyrinth	0	2		
Endocrine				
Eye	2	0		
GI	3	13***,&&		
General & Admin site	3	5		
Hepatobiliary				
Immune System	0	1		
Infection/Infestation	9	4		
Injury/Poison/Procedures	0	1		
Investigations				
Metabolism & Nutrition				
Musculoskeletal & Connective Tissue	9	4		
Neoplasms	1****	2		
Nervous System	3#	4		
Pregnancy/Perinatal				
Psychiatric	1	1		
Renal/Urinary	3	2		
Reproductive/Breast				
Respiratory/Thoracic/Mediastinal	6	9		
Skin/subcutaneous	5	5		
Surgical/medical procedures	4&	2##		
Vascular disorders	6	8		

**CSR lists severity of only GI adverse events (Table 15 CSR)*
***2 of the 5 adverse events in the NHP-554C arm were SAEs (myocardial infarction, syncope); 1 of the 4 adverse events in the IR-ASA arm was an SAE (angina pectoris).*
****1 of the 13 adverse events was an SAE (bright red blood per rectum). A review of the tables/listing yielded 13 adverse events in the GI SOC of the IR-ASA arm, whereas CSR content specified 14 adverse*

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events. The event "H Pylori" may have been categorized as GI whereas it was classified here an Infection. The term "vomiting/hematemesis", not listed in the CSRs adverse event table but mentioned in the CSR content, may have been the 14th adverse event.
*****breast cancer SAE*
*1 of the 3 adverse events was a SAE (TIA)*
##*1 of the 2 adverse events was a SAE ("circumcision balanitis erotica obliterans")*
& *1 of the 4 adverse events was a SAE ("hospital admission for cardiac catheterization"). In the absence of a description suggesting acute coronary syndrome, it was this reviewer's clinical judgment to assign this event to Procedure.*
&& *"Vomiting / Hematemesis" was described in a narrative as a SAE in the IR-ASA arm, but there was no corresponding adverse event listing in the CSR. Therefore, this SAE was added in this review to the SAE count.*
Source of Seriousness Criteria: CSR Table 14; source of Severity Criteria: CSR Table 15; source of Adverse Event listing: CSR Table 12.

9.15 Safety Data from Study U5A-97-02-003

Drug Treatment 6 Weeks	**NHP-554C 162.5 mg**	**IR-ASA 150 mg**	**Placebo**
Sample Size	37	40	37
Adverse Events (AE)	19	36	32
Severity of AE			
-mild	4*	10*	2*
-moderate	2*	7*	10*
-severe	0	0	2*
SAE	0	0	0
Death			
MedDRA SOC			
Blood and Lymphatic			
Cardiac	0	1	0
Congenital			
Ear and Labyrinth			
Endocrine			
Eye	0	0	1
GI	6	16	13
General & Admin site	0	1	2
Hepatobiliary	2	2	0
Immune System			
Infection/Infestation	5	4	6
Injury/Poison/Procedures	0	1	0
Investigations			
Metabolism & Nutrition			
Musculoskeletal & Connective Tissue	0	1	3
Neoplasms			
Nervous System	4	6	3
Pregnancy/Perinatal			
Psychiatric			
Renal/Urinary	0	3	0
Reproductive/Breast			
Respiratory/Thoracic/Mediastinal	0	0	1
Skin/subcutaneous	0	1	2
Surgical/medical procedures	1	0	0
Vascular disorders	1	0	1

* Severity of adverse events was limited to the GI SOC. The 2 adverse events listed as severe in the placebo arm were Abdominal Pain and Vomiting.

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9.16 Safety Data from Study CLICR 29

Drug Treatment 1week→7 months	**NHP-554C 350 mg qd**	**Ticlopidine 250 mg bid**		
Sample Size	119	113		
Adverse Events (AE)	88	89		
Severity of AE	Not reported	Not reported		
-mild				
-moderate				
-severe				
SAE	3	2		
Death	3	2		
MedDRA SOC				
Blood and Lymphatic	10	7		
Cardiac	25	20		
Congenital				
Ear and Labyrinth				
Endocrine	3	4		
Eye				
GI	24	31		
General & Admin site	19	14		
Hepatobiliary				
Immune System	3	9		
Infection/Infestation				
Injury/Poison/Procedures				
Investigations				
Metabolism & Nutrition				
Musculoskeletal & Connective Tissue				
Neoplasms				
Nervous System				
Pregnancy/Perinatal				
Psychiatric				
Renal/Urinary				
Reproductive/Breast				
Respiratory/Thoracic/Mediastinal	1	2		
Skin/subcutaneous				
Surgical/medical procedures				
Vascular disorders				

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9.17 Adverse Event Compilation for NHP-554C Exposed Subjects

Appendix Reference Number	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	9.10	9.11	9.12	9.13	9.14	9.15	9.16	Tot
Sample Size	95	50	50	12	72	24	44	25	12	48	13	32	186	37	119	819
Adverse Events (AE)	25	0	11	0	1	3	19	12	0	23	1	14	66	19	88	282
SAE												1	6		3	10
Death												1	1		3	5
MedDRA SOC																
Blood and Lymphatic						1									10	11
Cardiac												1	5		25	31
Congenital																0
Ear and Labyrinth			1													1
Endocrine															3	3
Eye												1	2			3
GI	5		1				7			7		4	3	6	24	57
General & Admin site	4		7				1	7					3		19	41
Hepatobiliary														2		2
Immune System															3	3
Infection/Infestation					1	1				1		1	9	5		18
Injury/Poison/Procedures	1									1	1					3
Investigations	4															4
Metabolism & Nutrition			1													1
Musculo-skeletal & Connective Tissue													9			9
Neoplasms													1			1
Nervous System	6					1	4			5		2	3	4		25
Pregnancy /Perinatal																0
Psychiatric													1			1

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Renal/Urinary							1			1			3			5
Reproductive /Breast							1									1
Respiratory /Thoracic /Mediastinal	5						5	5		7			6		1	29
Skin /Subcutaneous												2	5			7
Surgical /Medical procedures												1	4	1		6
Vascular disorders			1							1		1	6	1		10

Note: The Appendix reference number denotes the location of the study from which adverse event data were retrieved.

9.18 Adverse Event Compilation for IR-ASA Exposed Subjects

Appendix Reference Number	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	9.10	9.12	9.13	9.14	9.15	9.16*	Tot
Sample Size	97	0	25	12	24	24	44	24	12	13	66	196	40	113	690
Adverse Events (AE)	18	0	5	0	0	14	0	6	1	0	43	73	36	89	285
SAE											9	5		2	16
Death											2			2	4
MedDRA SOC															
Blood and Lymphatic			1			1						1		7	10
Cardiac								1			1	4	1	20	27
Congenital															0
Ear and Labyrinth						1					1	2			4
Endocrine														4	4
Eye															0
GI	3		1			6		1			6	13	16	31	77
General & Admin site	4		3			2						5	1	14	29
Hepatobiliary													2		2
Immune System												1		9	10
Infection/ Infestation						1					4	4	4		13
Injury/Poison/ Procedures												1	1		2
Investigations	1														1
Metabolism & Nutrition	1										1				2
Musculoskeletal & Connective Tissue	2										2	4	1		9
Neoplasms											1	2			3
Nervous System	4					3					2	4	6		19
Pregnancy/ Perinatal															0
Psychiatric	2										1	1			4
Renal/Urinary											1	2	3		6
Reproductive/ Breast															0
Respiratory/ Thoracic/ Mediastinal	1							4			6	9		2	22
Skin/subcutaneous												5	1		6

Surgical/medical procedures									1		6	2			9
Vascular disorders											2	8			10

* This study compared NHP-554C to ticlopidine.
Note: The Appendix reference number denotes the location of the study from which adverse event data were retrieved.

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9.19 Adverse Events as a Function of Dose and Time: NHP-554C

Adverse Events as a Function of Dose and Time for Subjects Administered NHP-554C (Number AE/Sample Size)								
Dose (mg)	Study	Single Dose	<1 week	1-2 wks	3 wks	4 wks	6 wks	Up to 7 mos
20	NHPASP01	7/20						
40	NHPASP01	5/19						
81	NHPASP01	0/18						
162.5	NHPASP01	8/18						
	CLICR 30			0/12				
	U5A9602001				9/24			
	U5A9602002					14/32		
	U5A9802004						66/186	
	U5A9702003						19/37	
	PKFT9542	0/50						
325	NHPASP01	5/20						
	ASA001	11/50						
	PKFT97101		1/24					
	ASA002			12/25				
	U5A9602001				14/24			
	CLICR 28					1/13		
	CLICR 29							88/119*
	PKCR0491	0/12						
650	PKFT97101	0/24						
	CLFT1039802		0/22					
975	PKFT97101	0/24						
	CLFT1029001	3/24						
1300	CLFT1039802		19/22					

** In the comparator arm of CLICR 29 (ticlopidine) there were 89 adverse events.*

9.20 GI Adverse Events as a Function of Dose and Time: NHP-554C

GI Adverse Events as a Function of Dose and Time for Subjects Administered NHP-554C (Number AE/Sample Size)								
Dose (mg)	Study	Single Dose	<1 week	1-2 wks	3 wks	4 wks	6 wks	7 mos
20	NHPASP01	1/20						
40	NHPASP01	2/19						
81	NHPASP01	0/18						
162.5	NHPASP01	2/18						
	CLICR 30			0/12				
	U5A9602001				4/24			
	U5A9602002					4/32		
	U5A9802004						3/186	
	U5A9702003						6/37 2/37 (Hepato-biliary)	
	PKFT9542	0/50						
325	NHPASP01	0/20						
	ASA001	1/50						
	PKFT97101		0/24					
	ASA002			0/25				
	U5A9602001				3/24			
	CLICR 28					0/13		
	CLICR 29							24/119
	PKCR0491	0/12						
650	PKFT97101	0/24						
	CLFT1039802		0/22					
975	PKFT97101	0/24						
	CLFT1029001	0/24						
	PKCR0491	0/12						
1300	CLFT1039802		7/22					

9.21 Adverse Events as a Function of Dose and Time: IR-ASA

Adverse Events as a Function of Dose and Time for Subjects Administered IR-ASA (Number AE/Sample Size)								
Dose (mg)	Study	Single Dose	<1 week	1-2 wks	3 wks	4 wks	6 wks	Up to 7 mos
5	NHPASP01	12/20						
10	NHPASP01	2/19						
20	NHPASP01	2/20						
40	NHPASP01	1/20						
75	U5A9602002					29/34		
81	NHPASP01	1/18						
150	U5A9602002					14/32		
	U5A9802004						72/196	
	U5A9702003						36/40	
160	CLICR 30			1/12				
325	ASA-001	5/25						
	PKFT 97101		0/24					
	ASA-002			6/24				
350	CLICR 28					0/13		
	PKCR 0491	0/12						
500	CLFT1029001	14/24						
600	CLFT1039802		0/22					
1200	CLFT1039802		0/22					

9.22 GI Adverse Events as a Function of Dose and Time: IR-ASA

GI Adverse Events as a Function of Dose and Time for Subjects Administered IR-ASA (Number AE/Sample Size)								
Dose (mg)	Study	Single Dose	<1 week	1-2 wks	3 wks	4 wks	6 wks	Up to 7 mos
5	NHPASP01	3/20						
10	NHPASP01	0/19						
20	NHPASP01	0/20						
40	NHPASP01	0/20						
75	U5A9602002					5/34		
81	NHPASP01	0/18						
150	U5A9602002					1/32		
	U5A9802004						13/196	
	U5A9702003						16/40 2/40 (hepatobiliary)	
160	CLICR 30			0/12				
325	ASA-001	1/25						
	PKFT 97101		0/24					
	ASA-002			1/24				
350	CLICR 28					0/13		
	PKCR 0491	0/12						
500	CLFT1029001	6/24						
600	CLFT1039802		0/22					
1200	CLFT1039802		0/22					

9.23 Gastrointestinal Adverse Events Description: NHP-554C and IR-ASA

Gastrointestinal Adverse Event Description						
	NHP-554C			IR-ASA		
Study (Appendix Reference)	Dose (mg) [Exposure Duration]	Number of Adverse Events	Descriptive Terms	Dose (mg) [Exposure Duration]	Number of Adverse Events	Descriptive Terms
NHP-ASP-01 (9.2)	20 [single dose]	1	Eructation	5	3	Nausea x 2 Abdominal Cramps
	40 [single dose]	2	Abdominal Discomfort x 2			
	162.5 [single dose]	2	Epigastric Pain Loose Stools			
ASA-001 (9.4)	325 [single dose]	1	Dyspepsia		1	Anorexia
CLFT1029001 (9.7)	500 [single dose]	0		500	6	Gastrointestinal Trouble x3 Nausea x3
CLFT1039802 (9.8)	1300 [< 1 wk]	7	Dyspepsia x 3 Nausea Vomiting Gastroenteritis Abdominal Pain			
ASA-002 (9.9)	325			325	1	Increased salivation
U5A9602001 (9.11)	162.5 [3wks]	4	Abdominal Pain x 3 Diarrhea			
	325 [3 wks]	3	Diarrhea Abdominal Pain x 2			
U5A9602002 (9.13)	162.5 [4 wks]	4	Dyspepsia x 2 Nausea x 2	75 [4wks] 150[4wks]	75mg: 5 150mg: 1	75mg: Dyspepsia Nausea x 2 Diarrhea Vomiting 150mg: Nausea

U5A9802004 (9.14)	162.5 [6 wks]	3	Constipation x 2 Blood per rectum	150(6wks)	13	Constipation x 3 Blood per rectum **(SAE)** Diarrhea x 2 Gastric Ulcer x 2 Gastroenteritis x 2 Eructation Flatulence Reflux
U5A9702003 (9.15)	162.5 [6 wks]	8	Abdominal Pain x 4 Dyspepsia x 2 Hepatobiliary x 2	150[6wks] Placebo [6 wks]	IR150mg : 18 Placebo : 13	IR 150mg: Abdominal Pain x 7 Dyspepsia Diarrhea x 3 Vomiting x 3 Nausea x 2 Hepato – Biliary x 2 Placebo: Abdominal Pain x 3 Dyspepsia Diarrhea Vomiting x 3 Nausea x 3 Flatulence x 2
CLICR 29 (9.16)	325 [7 mos]	24	GI-SOC: no specific terms	Ticlopidine 250mg bid [7 mos]	31	GI-SOC: no specific terms

9.24 Deaths

Deaths							
		NHP-554C			IR-ASA		
Study	Appendix Reference	Dose (mg x time)	Number of Deaths	Narrative	Dose (mg)	Number of Deaths	Narrative
U5A9602002	9.13	162.5 x 28d	1	Pt 57: 58 y/o male out-of-hospital died of cardiac arrest 3 weeks post last dose-no diagnosis	150 x 28d 75x28d	2	IR-ASA 150 mg Pt 54: 76 y/o male died of acute coronary syndrome 10 days post last dose. IR-ASA 75 mg Pt 107: 60 y/o (gender unknown) died of sub-arachnoid hemorrhage 11 days post last dose
U5A9802004	9.14	162.5 x 6 wks	1	Pt UK0089-543: 90 y/o male died due to Alzheimer disease 3 weeks post start of study	150 x 6 wks	0	
CLICR 29*	9.16	350 x 7 mos	3	Pt 5: 81 y/o male died due to ruptured thoracic aortic aneurysm 6 weeks post start of study Pt 265: 81 y/o male with heart failure and metastatic prostate cancer 2 weeks post start of study	250bid x 7mos	2	Pt 184: 76 y/o male died of neutropenic pulmonary infection 6 weeks post start of study Pt 27: 71 y/o male died of heart failure 6 weeks post start of study

				Pt 332: 54 y/o male alcoholic died of myocardial infarction on day of randomization			

** The active control in CLICR 29 was ticlopidine 250 mg bid*

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9.25 Withdrawals: U5A-96-02-002

Withdrawals: U5A-96-02-002 (Drug Phase, Drug, Dose, and Reason for Withdrawal)							
Run-In: Pre-treatment	Reason	NHP-554C 162.5 mg N=32	Reason	EC- IR-ASA 75 mg N=34	Reason	EC-IR-ASA 150 mg N=32	Reason
3	Protocol Violation (x 3)	3	Adverse Event (x 3)	1	Adverse Event	4	Adverse Event (x 1) Protocol Violation (x 3)

Source of Data: CSR Table 11, and CSR Appendix 2 Table 2

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9.26 Withdrawals: U5A-98-02-004

Withdrawals: U5A-96-02-004 (Drug, Dose, and Reason for Withdrawal)			
NHP-554C 162.5 mg N=186	Reason	EC-IR-ASA 150 mg N=196	Reason
50	Adverse Event (x27) Protocol Violation (x 14) Non-Compliance (x 6) Death (x 1) Lost-to-Follow-Up (x 2)	52	Adverse Event (x 21) Protocol Violation (x 13) Non-Compliance (x 15) Death (none) “Failure to Return” (x 3)

Source of Data: CSR Appendix 2 Table 2

9.27 Withdrawals: CLICR 29

Withdrawals: CLICR 29 (Drug, Dose, and Reason for Withdrawal)			
NHP-554C 350 mg qd N=119	Reason	Ticlopidine 250mg bid N=113	Reason
30	Adverse Event (x16) Protocol Violation (x 3) Reason Unspecified (x 10) Lack of Efficacy (x1)	23	Adverse Event (x 13) Protocol Violation (x 2) Reason Unspecified (x 5) Lack of Efficacy (x3)

Source of Data: CSR, section V.4.2 extraction of content

9.28 Literature Review/References

Guidance for Industry: Drug –Induced Liver Injury: Premarketing Clinical Evaluation, 2009, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Dug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER)

Taubert, K, 2008, Can patients with cardiovascular disease take nonsteroidal anti-inflammatory drugs, Circulation, 117: e322-324

Zhang, J, et al., 2014, Changes in plasma levels of vasoactive factors in patients undergoing abdominal surgery, Surgical Science, 5: 389-396

9.29 Labeling Recommendations

The proposed label should be as per aspirin monogram with the inclusion of NHP-ASP-01 pharmacokinetic and pharmacodynamic data in section 12.

9.30 Advisory Committee Meeting

No Advisory Committee Meeting.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FORTUNATO F SENATORE
04/30/2015

MARTIN ROSE
04/30/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 200671 **Applicant: New Haven Pharmaceuticals** **Stamp Date: September 5, 2014**

Drug Name: DURLAZA **NDA/BLA Type: 505b2**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	From correspondence to the Applicant dated 30 AUG 2013, the Division agreed that the text portion of the safety summary (module 2.7.4) would be sufficiently detailed to serve as the ISS. A PDF of the Safety Summary is included amongst several PDF summaries in module 2.7.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	From correspondence to the Applicant dated 30 AUG 2013, the Division agreed that the studies conducted with NHP-554C were primarily designed to evaluate and compare PK, PD, safety and tolerability between

Reference ID: 3649422

	Content Parameter	Yes	No	NA	Comment
					NHP-554C and a reference product (i.e. delayed or immediate release aspirin), and thus an ISE would not be generated.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2.5 (Clinical Overview, section 6)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b) (2)			Reference drug is Immediate Release aspirin capsules
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: NHP-ASP-01 Study Title: Phase 1 Open-Label, Four-Way, Randomized, Crossover, Single dose, Dose-response study comparing the pharmacodynamics and pharmacokinetics of NHP-554-C capsules to immediate-release aspirin capsules in healthy volunteers Sample Size: total 50 Arms: two arms each subdivided into 5 dosing arms, respectively. Location in submission: 5.3.4.1	X			See section 9.4.4. of NHP-ASP-01 CSR. NHP-554-C doses of 20, 40, 81, 162.5, and 325mg were compared to IR aspirin capsules at doses of 3, 10, 20, 40, and 81mg representing 10% →100% inhibition of TxB2 and 11-dehydro-thromboxane B2 production, and platelet aggregation at 24 hours post-dose. The dose-selection strategy was based on the Applicant's rationale that the doses of NHP-554-C will produce a PD profile similar to that of IR aspirin at corresponding IR doses.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	The basis of the NDA is a single PK-PD study comparing various doses of NHP-ASP-01 to IR aspirin. The Applicant's strategy is similar to the development of a generic drug.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the	X			The pivotal study appears to be well-controlled to the extent

Reference ID: 3649422

	Content Parameter	Yes	No	NA	Comment
	Division) for approvability of this product based on proposed draft labeling?				agreed to with the Applicant by the Division.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			See Minutes by the Division dated 30AUG 2013.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Foreign data came from supportive studies conducted in France, Germany, and Great Britain, but the basis of approval is the one study conducted in the US.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			ECGs at pre-dosing and at study-specific post-dosing intervals were collected from various studies (i.e. NHP-ASP-01, ASA-001, PKFT-9542, and CLICR-30)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Module 2.7.4 in lieu of an ISS as per agreement with the Division.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	Based on a brief review of the NDA package, I summed up the number of subjects who were reported to complete the various studies they were enrolled in. I counted 543 subjects receiving NHP-ASP-01who completed their respective studies. Of these, 129 received a SD (24 at 162.5mg; 82 at 325mg, 23 at 975mg); 22 received 5 days of 1300mg/day; 24 received 7 days of 325mg/day; 24

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
					received 9 days of 325mg/day; 11 received 10 days of 162.5mg/day; 23 received 3 weeks of 325mg/day; 31 received 4 weeks of 162.5mg/day; 12 received 4 weeks of 325mg/day; 170 received 6 weeks of 162.5mg/day; and 97 received 13 months at 325mg/day. Based on the guidelines, the Applicant met the criteria for the 1 year exposure at the efficacious dose for their formulation. Since the active drug is aspirin, there is a large exposure to the general population.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			In the pivotal NHP-ASP-01 trial, the Applicant provided the MedDRA SOC / MedDRA PT / Verbatim Terms for each of the listed adverse events (listing 16.2.7.1). However, the Applicant stated in section 2.1.1 of the Summary of Clinical Safety (Module 2.7.4) that the supportive studies, mostly conducted in the 1990s, were coded using different dictionaries. In some cases, only the investigators' verbatim terms were provided.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
					The information requested on the CRFs associated with an AE was not consistently captured in all studies (e.g. study drug relatedness, severity).
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			The Applicant included a focused analysis on GI Safety Data from supportive studies CKICR-28, CLFT-103-9802, U5A-97-02-003 and U5A-96-02-001.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Narratives are located in section 3.6 of the summary of clinical safety (module 2.7.4). Deaths are located in section 3.6.1 of summary of clinical safety and withdrawals due to adverse events are located in section 3.6.3 of the summary of clinical safety. Narratives for SAEs were also included (section 3.6.2 of the summary of clinical safety).
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			The Applicant submitted the electronic dataset for the food effect study (ASA-001) as requested by the Division as per Minutes dated 30AUG2013.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The Applicant documented in module 1.9 that the pediatric waiver was granted. Based on filing meeting, this should be verified.
ABUSE LIABILITY					

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	Content Parameter	Yes	No	NA	Comment
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	There are supportive studies conducted in France, Germany, and Great Britain, but the basis of approval is the one study conducted in the US.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	The Applicant's dataset supports the PK-PD profile for NHP-554C vs IR ASA. The applicant wishes to apply the indications for aspirin to NHP-554-C, thereby rendering the NDA similar to that of a generic.
34.	Are all datasets to support the critical safety analyses available and complete?	X			The datasets are as complete as possible given the legacy status of the supportive studies.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			The Applicant submitted legacy CRFs (some written in French) from supportive studies. The Applicant submitted the CRFs from one subject in the pivotal NHP-ASP-01 study. This subject was discontinued due to an NHP-554-C related liver adverse event (elevated AT 7-10xULN; AP 1.3xULN; TB wnl). There are no other CRFs in this submission. There were no reported

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	Content Parameter	Yes	No	NA	Comment
					deaths in the NHP-ASP-01 study. In my opinion, it is acceptable to not have all CRFs in the original submission in lieu of requesting them during the review process if deemed necessary.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	Division did not make previous requests.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			See Module 1
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Located in the title page of NHP-ASP-01 CSR

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Fred Senatore MD, PhD, FACC — 23OCT2014

Reviewing Medical Officer — Date

Clinical Team Leader — Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3649422

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FORTUNATO F SENATORE
10/28/2014

THOMAS A MARCINIAK
10/28/2014