CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200671Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY ADDENDUM

NDA	200671
Submission date	September 5, 2014
Submission type	Original, 505(b)(2) – Standard Review
Brand Name	DURLAZA
Applicant	New Haven Pharmaceuticals
Formulation	Oral extended release micro-particles in a capsule
Dosing regimen	162.5 mg once-daily
Indication	Secondary prevention of thrombotic CV events following an ischemic stroke, TIA, MI or angina pectoris
Review Division(s)	Division of Clinical Pharmacology – 1 (OCP) Division of Cardiovascular and Renal Products (OND)
Primary Reviewer	Sudharshan Hariharan, Ph.D.
Secondary Reviewer	Rajanikanth Madabushi, Ph.D.

Background

DURLAZA is an extended release formulation of aspirin. Results from NHP-ASP-01, a study which evaluated the dose-pharmacodynamic response of DURLAZA, are critical for regulatory action as they provide the bridge to immediate release aspirin 81 mg. The Office of Study Integrity and Surveillance (OSIS) performed inspection of the bioanalytical assay site pertaining to this study and found limitations (review DARRTS date: 06/18/2015). The inspection identified cross-reactivity with structurally similar analogs in the ELISA method used for bioanalysis of serum thromboxane B_2 (TxB_2) and urinary 11-dehydro-TxB_2. The OSIS review concluded that their findings may affect the ability to interpret pharmacodynamic data from study NHP-ASP-01. These findings were communicated to the applicant and they responded in making a case that the issue of cross-reactivity does not impact study results and in turn deriving a dose of DURLAZA that is equivalent to that of immediate release aspirin 81 mg. This memo is in response to the supportive information submitted by the applicant.

Recommendation

Following review of the information submitted by the applicant, DCP-1 concludes that the issue of cross-reactivity with the ELISA method for bioanalysis of serum TxB_2 and urinary 11-dehydro-TxB_2 does not significantly impact the results of study NHP-ASP-01 due to reasons summarized in this memo. Therefore, a bridge between DURLAZA and immediate release aspirin 81 mg can be established as originally summarized in the clinical pharmacology review (DARRTS date: 06/02/2015).

Summary of the issue raised by OSIS

The (b) (4) kits (marketed by (b) (4)) used for the bioanalysis of TxB_2 and 11-dehydro-TxB_2 indicated cross-reactivity to structurally similar moieties as shown in Table 1 (Appendix). Cross-reactivity to TxB_2 by thromboxane B_3 (TxB_3) and 2, 3-dinor-TxB_2 was 200% and 9.9%, respectively; and cross-reactivity to 11-dehydro-TxB_2 by 11-dehydro-2, 3-dinor-TxB_2 was 330%. As quality control samples during assay validation were prepared in charcoal stripped serum or

urine, the OSIS review concluded that the validation of assays cannot be ensured as the issue of cross-reactivity or matrix effect were not accounted. The review also found pharmacokinetic data from study NHP-ASP-01 to be reliable and acceptable for review.

Summary of information submitted by the applicant

The following points were made by the applicant in response to the issue of cross-reactivity and the interpretability of the data from study NHP-ASP-01 to which the reviewer is largely in agreement with:

- 2, 3-dinor TxB_2 and 11-dehydro-2, 3-dinor TxB_2 are metabolites of TxB_2. Any interference by these moieties should not significantly impact the pharmacodynamic response to aspirin as they are simply metabolites of TxB_2.

  Reviewer's note: A schematic of the major metabolites of TxB_2 is shown in Figure 1 (Appendix). 2, 3-dinor TxB_2 and 11-dehydro-2, 3-dinor TxB_2 are β-oxidation products of TxB_2 and 11-dehydro TxB_2, respectively. Since 2, 3-dinor TxB_2 and 11-dehydro-2, 3-dinor TxB_2 are further downstream metabolites of TxB_2, any interference by these metabolites should not significantly affect pharmacodynamic response to aspirin as measured in this study (i.e., percent change from baseline) for both treatment arms – DURLAZA and immediate release aspirin. This is consistent with the primary approach of utilizing TxB_2 as the pharmacodynamic marker for aspirin's effect on TxA_2 inhibition (metabolically unstable).

- According to the applicant, the diet of study participants generally did not constitute a significant amount of fish oil, which is a precursor for generation of TxB_3. Therefore, cross-reactivity due to TxB_3 in the bioanalysis of TxB_2 in this study is expected to be minimal.

  Reviewer's note: TxB_3 is a product in the cyclooxygenase metabolic pathway of eicosapentaenoic acid (Figure 2, Appendix) analogous to the formation of TxB_2 through the cyclooxygenase pathway of arachidonic acid. A few publications report the endogenous levels of eicosapentaenoic acid (C20:5ω3, precursor for TxB_3) in comparison to the levels of arachidonic acid (C20:4ω6, precursor to TxB_2), prior to and following a fish oil rich diet[1,2,3]. In the absence of a fish oil rich diet, the levels of eicosapentaenoic acid are 7-fold (in plasma) and 44- to 65-fold (in platelet phospholipid) lower than arachidonic acid. Further, the publication by Hamazaki et al[4], which measured urinary TxB_3 relative to TxB_2 in two healthy subjects before and after a fish oil rich diet shows that the level of urinary TxB_3 is 20- to 50-fold lower when compared to TxB_2. In another publication[5], the levels of 11-dehydro-TxB_3 (a metabolite of TxB_3) in urine is reported to be less than 1% of that of 11-dehydro-TxB_2 prior to supplementation with eicosapentaenoic acid. Therefore, based on these literature reports it is reasonably evident that the endogenous levels of TxB_3 relative to TxB_2 in serum would be significantly lower in the absence of eicosapentaenoic acid supplementation. In the current study, the recruited healthy volunteers are from a geographic location (Connecticut, USA) where they are not expected to be on a fish oil rich diet. The applicant states that the subjects enrolled for the study were not on

[1] Fischer S, Weber PC. Biochem Biophys Res Commun. 1983 Nov 15;116(3):1091-9

[2] Fischer S et al. Prostaglandins. 1986 Aug;32(2):235-41

[3] von Schacky C et al. J Lipid Res. 1985 Apr;26(4):457-64

[4] Hamazaki T et al. Biochem Biophys Res Commun. 1988 Mar 30;151(3):1386-94

[5] Mizugaki M et al. Rapid Commun Mass Spectrom. 1995;Spec No:S55-S60

any fish oil OTC supplements or herbs. Moreover, following study drug administration, the subjects were provided with a standard meal which is not expected to contain fish based diet. Therefore, cross-reactivity due to TxB_3 affecting the bioanalysis of serum TxB_2 can be assumed to be minimal, thereby having negligible impact on interpretation of the results from study NHP-ASP-01.

- The issue of cross-reactivity, if any, should affect both immediate release aspirin and DURLAZA to the same extent.

  Reviewer's note: The issue of cross-reactivity or matrix effect impacting results of study NHP-ASP-01 seems to be minimal from the points summarized above. Moreover, as aspirin is the underlying pharmacological species in DURLAZA and immediate release formulation, any cross-reactivity in the measurement of serum TxB_2 or urinary 11-dehydro-TxB_2 cannot be different between the two treatment arms evaluated in study NHP-ASP-01. Therefore, the ability to bridge DURLAZA to immediate release aspirin 81 mg based on a 2-fold difference in ID_{50} between the two treatments could not seem to have been impacted by the issue of cross-reactivity.

Further, the use of pharmacodynamic measures to identify the dose of DURLAZA was primarily due to the applicant's assertion that systemic levels of acetyl salicylic acid would not be reliably measurable with their product (see Section 2.1.2 of clinical pharmacology review DARRTS date: 06/02/2015). However, upon conduct of the study the applicant was able to quantify plasma acetyl salicylic acid levels and allow for comparison of PK measures between DURLAZA and IR aspirin (see Section 2.4.1 of review DARRTS date: 06/02/2015). It should be noted that PK findings were found acceptable in OSIS review. The results of the PK and PD are reasonably aligned and provide additional support for reliance on the PD findings.

APPENDIX

Table 1: Specificity of the Thromboxane B_2 (A) and 11-dehydro Thromboxane B_2 (B) (b) (4) kit (supplied by (b) (4)) used for the analysis of samples in study NHP-ASP-01 (species with cross-reactivity <5% are not listed in this table).

(A) Thromboxane B_2

Compound	Cross-reactivity
Thromboxane B_2	100%
Thromboxane B_3	200%
2,3-dinor Thromboxane B_2	9.9%

(B) 11-dehydro Thromboxane B_2

Compound	Cross-reactivity
11-dehydro Thromboxane B_2	100%
11-dehydro-2,3-dinor Thromboxane B_2	330%

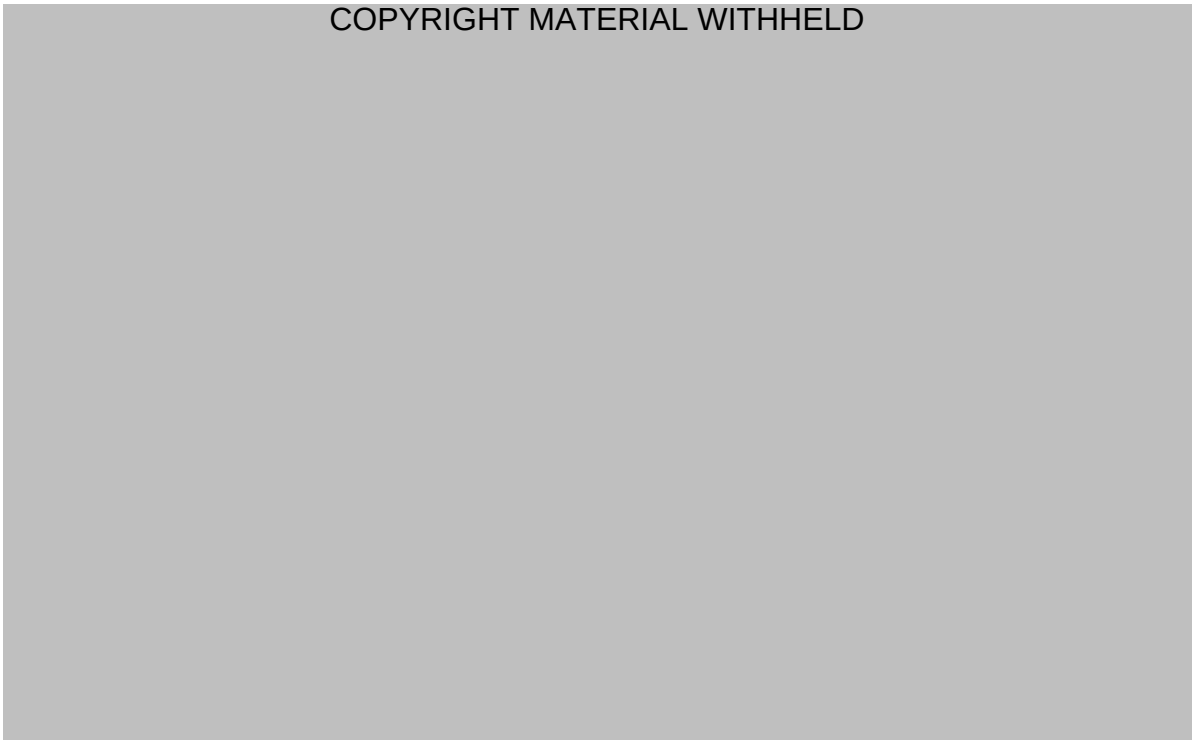

Figure 1: Major routes of metabolism of Thromboxane B_2[6]

[6] Needleman P et al. Proc Natl Acad Sci U S A. 1979 Feb; 76(2): 944-8

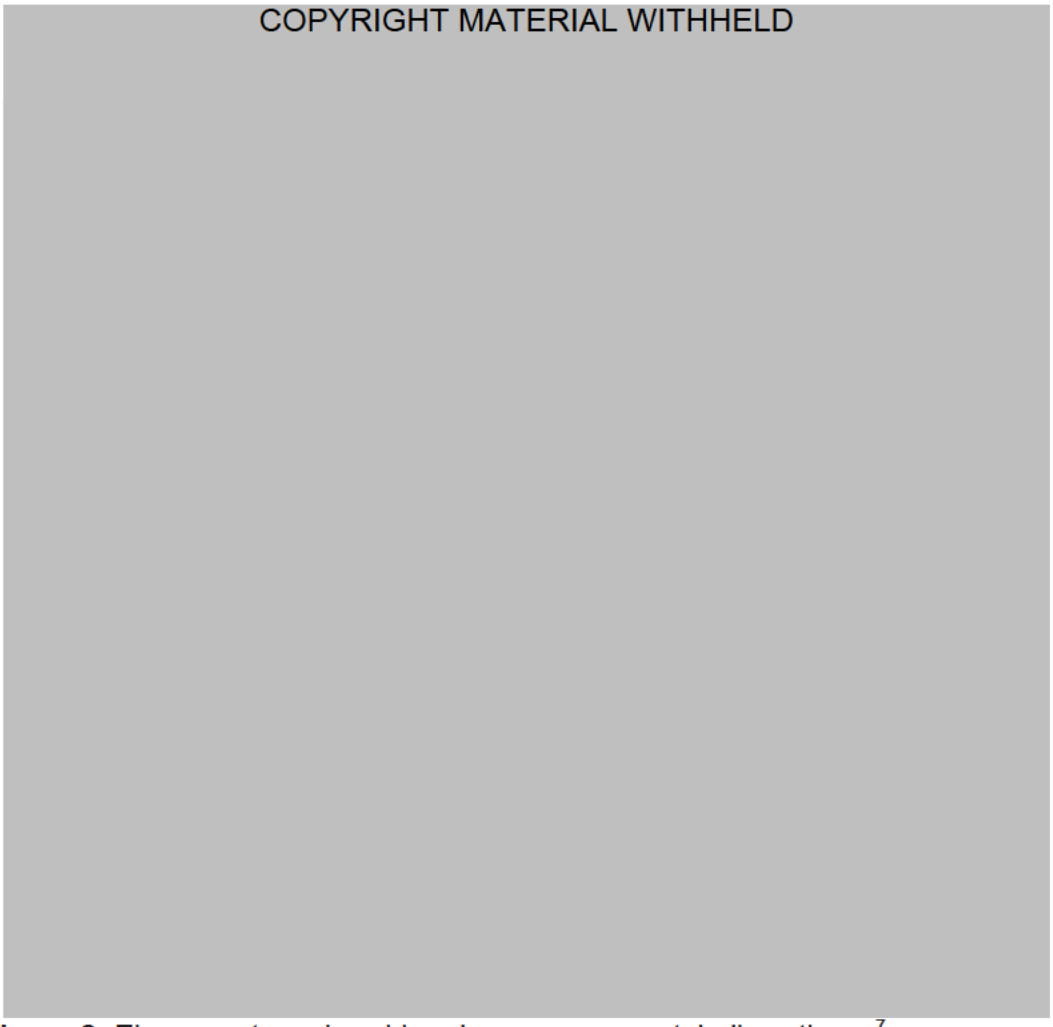

Figure 2: Eicosapentaenoic acid cyclooxygenase metabolic pathway[7]

[7] Catella F et al. Proc Natl Acad Sci U S A. 1986 Aug; 83(16): 5861-5

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/s/

SUDHARSHAN HARIHARAN
08/07/2015

RAJANIKANTH MADABUSHI
08/08/2015

MEHUL U MEHTA
08/08/2015

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	200671
Submission Date	September 5, 2014
Submission Type	Original, 505(b)(2) – Standard Review
Brand Name	DURLAZA
Generic Name	Aspirin
Sponsor	New Haven Pharmaceuticals
Therapeutic Class	Anti-platelet agent
Formulation	Oral controlled release micro-particles in a capsule
[Strength]	[162.5 mg]
Dosing Regimen	162.5 mg once-daily
Proposed Indication	Secondary prevention of thrombotic CV events following an ischemic stroke, TIA, MI or angina pectoris
OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
Reviewer	Sudharshan Hariharan, Ph.D.
Team Leader	Rajanikanth Madabushi, Ph.D.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
ASA	Acetyl Salicylic Acid
AUC	Area Under Curve
CI	Confidence Interval
C_{max}	Peak Concentration
COX-1	Cyclooxygenase-1
CV	Cardiovascular
DCP1	Division of Clinical Pharmacology 1
DSC	Drug Safety Communication
ELISA	Enzyme Linked Immunosorbent Assay
GMR	Geometric Mean Ratio
IQR	Inter Quartile Range
ISR	Incurred Sample Reanalysis
LC	Liquid Chromatography
LLOQ	Lower Limit of Quantification
LS	Least Square
MI	Myocardial Infarction
MS	Mass Spectrometry
OCP	Office of Clinical Pharmacology
OND	Office of New Drugs
OSI	Office of Scientific Investigations
PD	Pharmacodynamics
PK	Pharmacokinetics
QBR	Question Based Review
QC	Quality Control
SA	Salicylic Acid
SAE	Serious Adverse Event
$t_{1/2}$	Elimination Half-Life
TIA	Transient Ischemic Attack
TxA_2	Thromboxane A_2
TxB_2	Thromboxane B_2

1. EXECUTIVE SUMMARY

New Haven Pharmaceuticals, Inc. is seeking approval for DURLAZA, a capsule containing controlled release microparticles of ASA, via the 505(b)(2) pathway for secondary prevention of thrombotic CV events. The dosing regimen for NHP-554C as proposed by the applicant is 162.5 mg once-daily which is expected to result in pharmacodynamic effects similar to that following IR aspirin 81 mg. The applicant relies on the publicly available data in over-the-counter (OTC) aspirin monograph, professional labeling (21 CFR Part 343.80) for efficacy and safety supporting the proposed indication.

The drug product was originally developed by Flamel Technologies, France under the brand name Asacard®. Asacard® 162.5 mg was approved by the EMA in 1998 for secondary prevention of CV disease, but was never commercialized in any country. Early clinical development was conducted in Europe prior to acquisition of this drug product by New Haven Pharmaceuticals in 2009. There are three clinical pharmacology studies which support dosing and inform labeling: (1) NHP-ASP-01 (pivotal dose finding trial – performed by New Haven Pharmaceuticals, Inc.), (2) ASA-001 (food effect study) and (3) CLICR-30 (effect on vascular and platelet prostaglandins upon repeat dosing).

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP1) finds the bridging information from Study NHP-ASA-01 acceptable and recommends approval of DURLAZA 162.5 mg pending the findings from bioanalytical site inspection.

1.2 Phase 4 Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

- A comparison of the dose-PD (inhibition of serum TxB_2 and urinary 11-dehydro-TxB_2) relationship indicates ~2-fold higher ED_{50} for NHP-554C relative to IR aspirin. Based on this information, a dose of NHP-554C 162.5 mg would result in similar pharmacodynamic effects compared to that achieved by IR aspirin 81 mg.

- Pairwise data comparison indicates that the mean inhibition of serum TxB_2 following the first dose of NHP-554C 162.5 mg is lower than that observed following IR aspirin 81 mg. However, upon repeat administration of NHP-554C 162.5 mg, the inhibition of serum TxB_2 reach near maximal values. Due to time taken to reach maximum PD effect, the proposed label includes a warning not to administer DURLAZA when a rapid onset of action is required (e.g., acute treatment of MI or (b) (4)).

- A high fat meal has been shown to further prolong the absorption of ASA from the drug product resulting in a delayed T_{max} (median = 4.0 h), modest increase in C_{max} (1.4-fold) and approx. 3-fold higher AUC, compared to when administered under fasted condition. The increase in

exposure to ASA in the presence of a high fat meal is approx. 2-fold higher when compared to exposures resulting from IR aspirin 81 mg. Though there is clinical experience for an increase in ASA exposure of this magnitude, however, the controlled release characteristics of the product are altered. Therefore, DURLAZA should preferably be administered in a fasted state.

- (b) (4)

- When concomitant use with ibuprofen is warranted, ibuprofen should be administered at least 2 to 4 h after NHP-554C dosing. Also, at least 8 h should elapse after ibuprofen dosing, before administering aspirin, to avoid significant interference. When twice-a-day or more frequent regimen for ibuprofen is warranted, this combination may not be used together.

2. QUESTION BASED REVIEW

Note: Aspirin is marketed under the monograph. Please refer to 21CFR343.80 for comprehensive prescribing information for aspirin including relevant clinical pharmacology literature and clinical studies supporting the proposed indications. Therefore, an abridged version of the question based review is used to address the clinical pharmacology issues pertinent to this drug product.

2.1 General Attributes of the Drug Product

2.1.1 What are the features of the drug product?

DURLAZA is a capsule containing controlled release microparticles (b) (4) (b) (4). The (b) (4) acts as a semi-permeable membrane enabling controlled release of ASA from the microparticles. Other components of this drug product are – castor oil (b) (4), magnesium stearate (b) (4), tartaric acid (b) (4) (b) (4) colloidal silica (b) (4) and talc (b) (4)). For *in vitro* dissolution profile of this drug product in comparison to IR aspirin, please refer drug product quality review.

(b) (4) (b) (4) NHP-554C is another name for this drug product following its acquisition by New Haven Pharmaceuticals, Inc.

2.1.2 What is the applicant's rationale in developing this drug product?

The objective was to have a drug product that would sustain the release of ASA from the microparticles, resulting in prolonged absorption across the gastrointestinal tract. This was expected to result in lower systemic exposures to ASA (as pre-systemic metabolism would not be saturated), but with adequate levels in the portal vein, so as to have a similar platelet inhibition when compared to IR aspirin. (b) (4) (b) (4) (b) (4).

2.1.3 What is the regulatory history associated with the submission of this NDA?

The applicant met with the Division on multiple occasions to seek advice on the type of data that would be required for approval of their drug product. The aim was to derive a dose of NHP-554C that would be therapeutically equivalent to IR aspirin 81 mg. The Division did not accept therapeutic equivalence based on bioequivalence of PK measures, as NHP-554C was expected to have lower systemic exposure (both C_{max} and AUC) to ASA but with similar PD effects when compared to IR aspirin. Hence, the Division envisioned a dose-response study with comparison of ED_{50s} between NHP-554C and IR aspirin towards PD markers of importance to aspirin (serum TxB_2, urinary 11- dehydro-TxB_2 and platelet aggregation) to aid in deriving a dose of NHP-554C that would be therapeutically equivalent to IR aspirin 81 mg. As repeat dose administration and doses higher than 81 mg were going to decrease the ability to demonstrate dose-response and discriminate between the two products, the Division recommended the study to be performed at

doses that will allow the characterization of the dose-response relationship following single dose.

(b) (4)

2.1.4 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The generally accepted and well-understood mechanism by which aspirin reduces the risk of adverse CV events is through inhibition of platelet aggregation via irreversible acetylation of the COX-1. Inhibition of COX-1 prevents conversion of arachidonic acid to TxA_2, which a potent agonist of platelet aggregation and therefore of thrombosis. At higher doses, aspirin inhibits the synthesis of vasodilatory prostaglandins such as PGE_2, I_2 through the cyclooxygenase dependent pathway.

The proposed indication for DURLAZA is for secondary prevention of thrombotic CV events following an ischemic stroke, transient ischemic attack (TIA), myocardial infarction (MI), or angina pectoris. Specifically, DURLAZA is indicated to

- Reduce the risk of death and MI in patients with chronic artery disease such as patients with a history of MI or unstable angina pectoris or chronic stable angina
- Reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA

2.1.5 What are the PD moieties of interest for the antiplatelet activity of aspirin?

As TxA_2 is highly unstable and has an extremely short half-life (20-30 s), serum TxB_2 (biologically inactive and stable metabolite of TxA_2) and urinary 11-dehydro TxB_2 (metabolite of TxB_2 excreted in urine) are usually considered as a reliable markers of assessing platelet activity in response to aspirin. Inhibition of platelet aggregation *ex vivo* is also a common measure of the antiplatelet activity in response to aspirin therapy, but is generally subject to more noise.

2.1.6 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage for DURLAZA is 162.5 mg (based on pivotal study NHP-ASA-01) to be administered orally, preferably in a fasted state.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Three clinical pharmacology studies support dosing and inform labeling for DURLAZA [Table 1]. NHP-ASA-01 is a pivotal dose-response study that was performed to choose a dose of NHP-

55C that is pharmacodynamically equivalent to IR aspirin 81 mg. ASA-001 evaluated the impact of a high fat meal on the systemic bioavailability of Asacard®. CLICR-30 evaluated the impact of repeat dosing of Asacard® on vascular and platelet prostaglandins relative to immediate release aspirin.

Table 1: Design features of clinical pharmacology studies supporting this NDA

Study No.	Type	Design	Variables
NHP-ASA-01	Dose-response	Open-label, randomized, 4-way, crossover, single-dose *NHP-554C*: 20, 40, 81, 162.5, 325 mg *IR aspirin*: 5, 10, 20, 40, 81 mg	*PK*: ASA, SA *PD*: serum TxB_2, urinary 11-dehydro-TxB_2, platelet aggregation
ASA-001	Food effect	Open-label, randomized, 3-way, crossover, single-dose *Trt A*: 325 mg Asacard®, fasted *Trt B*: 325 mg Asacard®, fed *Trt C*: 325 mg Bayer®, fed	*PK*: ASA, SA *PD*: serum TxB_2
CLICR-30	Effect on vascular and platelet prostaglandins	Open-label, randomized, 2-way, crossover, multiple-dose *Trt A*: 162.5 mg Asacard®, once-daily for 10 days *Trt B*: 162 mg Kardegic®, once-daily for 10 days	*PK*: ASA, SA *PD*: serum TxB_2, urinary 11-dehydro-TxB_2, urinary dinor-6-keto-F1α

2.3 Basis for Regulatory Action

2.3.1 What is the basis for regulatory action for this drug product?

The regulatory action for DURLAZA is based on the results of the pivotal study NHP-ASA-01. The objective of this study was to compare the dose-response relationship of ASA between NHP-554C and IR aspirin in healthy subjects. The response measures selected were inhibition of serum TxB_2, inhibition of urinary 11-dehydro-TxB_2, and inhibition of platelet aggregation. The range of doses selected for IR aspirin were 5, 10, 20, 40 and 81 mg and for NHP-554C were 20, 40, 81, 162.5 and 325 mg. The doses for IR aspirin were selected so as to provide a range of responses between 10% and near maximal inhibition of serum TxB_2 and urinary 11-dehydro-TxB_2 following the first dose. NHP-554C doses were selected with an expectation that the respective dose levels would provide a similar PD effect after a single dose as those observed for IR aspirin. Primary PD parameter ED_{50} for inhibition of serum TxB_2, urinary 11-dehydro-TxB_2 and platelet aggregation was derived using an E_{max} model. Dose-response data was then fitted in an E_{max} model to yield the primary PD parameter ED_{50} using WinNonlin v5.3.

TxB_2 results: Figures 1 and 2 show the dose-response relationship for NHP-554C and IR aspirin towards serum TxB_2 and urinary 11-dehydro-TxB_2, respectively, using a sigmoid E_{max} model.

The PD parameters are shown in Table 2. It can be seen that the ED_{50} for inhibition of serum TxB_2 and urinary 11-dehydro-TxB_2 is 1.9-fold and 2.3-fold higher for NHP-554C when compared to IR-aspirin. Therefore, based on a 2-fold lower ED_{50}, NHP-554C 162.5 mg should be pharmacodynamically equivalent to IR aspirin 81 mg.

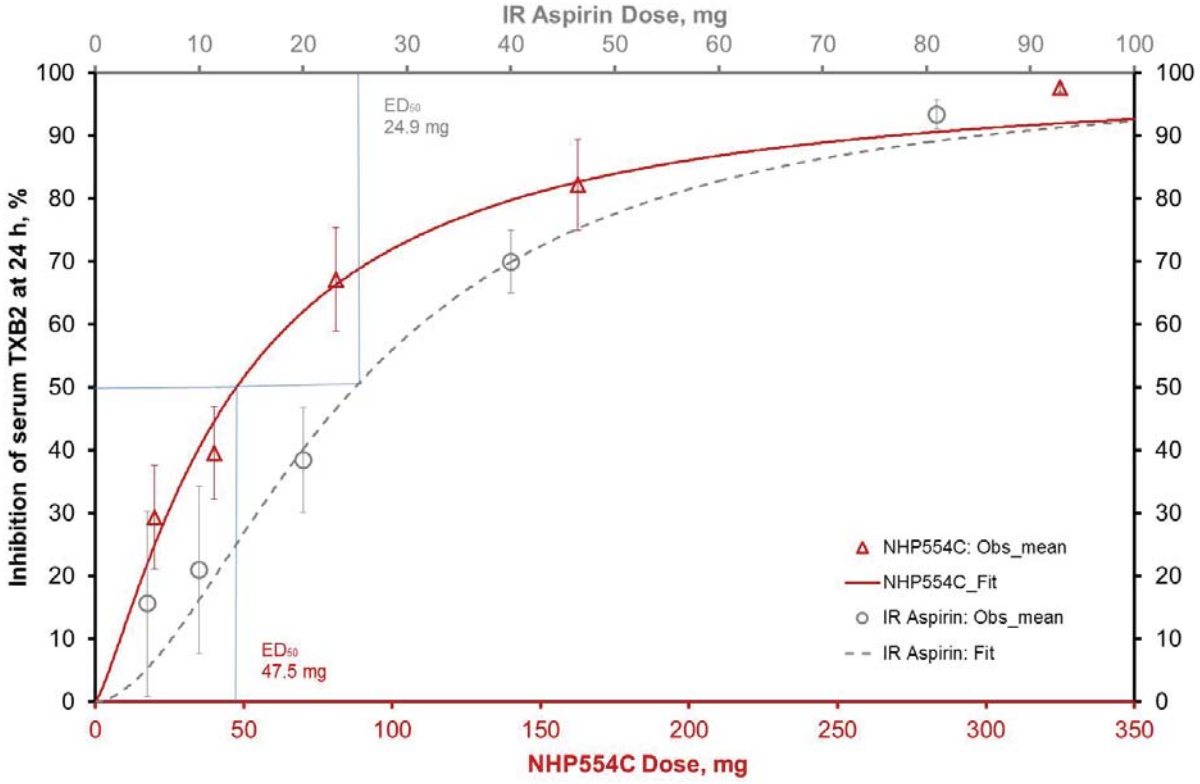

Figure 1: Inhibition of serum TxB_2 at 24 h post-dose following a single dose administration of NHP-554C (20, 40, 81, 162.5, or 325 mg) or IR aspirin (5, 10, 20, 40, or 81 mg). The plot is color coded to differentiate between NHP-554C (red) and IR aspirin (gray) treatment arms. The observed response variable is shown as mean ± SE, as represented by open triangles and circles (± error bars) for NHP-554C and IR aspirin, respectively. The sigmoid E_{max} model fit through the subject level data is represented by the red solid and gray broken lines for NHP-554C and IR aspirin, respectively.

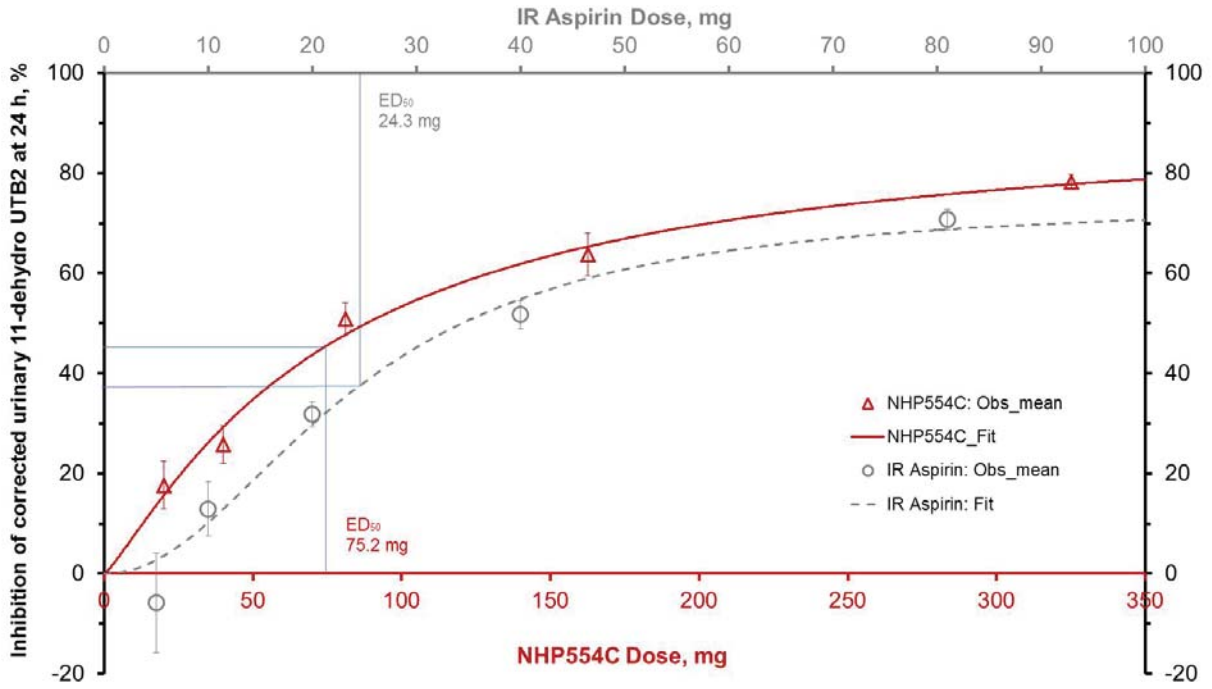

Figure 2: Inhibition of corrected urinary 11-dehydro-TxB_2 at 24 h post-dose following a single dose administration of NHP-554C (20, 40, 81, 162.5, or 325 mg) or IR aspirin (5, 10, 20, 40, or 81 mg). The plot is color coded to differentiate between NHP-554C (red) and IR aspirin (gray) treatment arms. The observed response variable is shown as mean ± SE, as represented by open triangles and circles (± error bars) for NHP-554C and IR aspirin, respectively. The sigmoid E_{max} model fit through the subject level data is represented by the red solid and gray broken lines for NHP-554C and IR aspirin, respectively.

Table 2: PD parameters for inhibition of serum TxB_2 and urinary 11-dehydro-TxB_2 between NHP-554C and IR aspirin. Data expressed as mean [CV%].

	PD parameter	IR aspirin	NHP-554C
Serum TxB_2	**E_{max}, %**	99.9 [24.7]	99.9 [17.6]
	ED_{50}, mg	24.9 [40.1]	47.5 [37.6]
	Gamma (γ)	1.79 [44.9]	1.26 [38.0]
Urinary 11-dehydro-TxB_2	**E_{max}, %**	90.0 [25.8]	91.2 [13.9]
	ED_{50}, mg	32.6 [41.6]	75.2 [30.5]
	Gamma (γ)	1.61 [34.1]	1.19 [22.2]

Platelet inhibition results: There was no inhibition of platelet aggregation in response to aspirin when collagen was used as agonist. This may be expected as aspirin specifically inhibits arachidonic acid mediated platelet aggregation. Inhibition of platelet aggregation in response to aspirin using arachidonic acid as agonist was highly variable, particularly NHP-554C 162.5 mg

and IR aspirin 81 mg dose groups (Figs. 4A and 4B in Individual Study Review NHP-ASA-01 , page 24). Due to highly variable results in these dose groups, no further analyses were conducted.

2.4 Pharmacokinetics

2.4.1 What are the PK characteristics of this drug product?

Compared to IR aspirin, the release of ASA from NHP-554C is sustained resulting in lower systemic exposures to ASA [Fig. 3]. The time to reach peak ASA concentration is marginally delayed following NHP-554C administration (median T_{max}: 1.75 h for NHP-554C vs 1 h for IR aspirin). The peak concentration of ASA following administration of NHP-554C is significantly blunted when compared to IR aspirin (mean C_{max}: approx. 80% lower). The area under the plasma concentration-time curve for ASA is approx. 37% to that following IR aspirin [Study NHP-ASA-001].

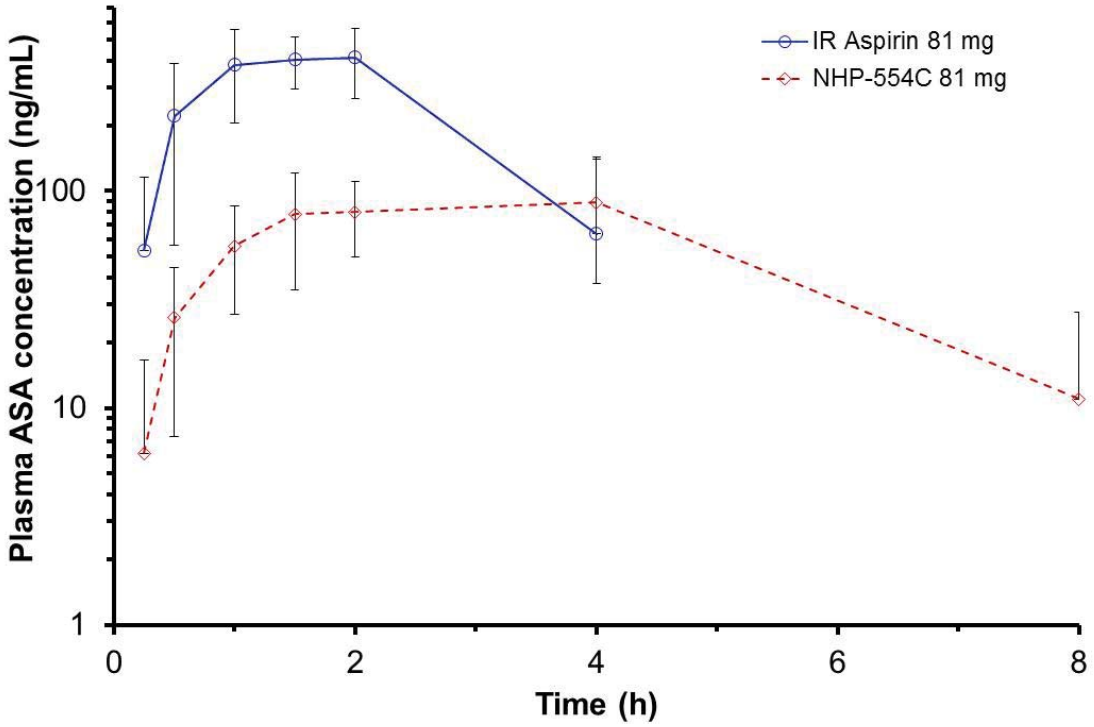

Figure 3: Plasma concentration-time course of ASA following IR aspirin 81 mg and NHP-554C 81 mg. Data expressed as mean ± SD.

Systemic exposure (AUC) to ASA increases with increasing doses following administration of NHP-554C (dose range: 20 to 325 mg) with a trend for more than proportional dose increase. This apparently more than proportional increase in AUC with increase in dose may be due to the limited number of quantifiable ASA concentrations at the lower dose levels. The between-subject variability in the PK measures of ASA following NHP-554C is about 30 to 40%. There is no data to comment about the within-subject variability of ASA from this drug product.

2.5 Pharmacodynamics

2.5.1 What are the PD characteristics of this drug product?

The mean inhibition of serum TxB_2 following NHP-554C 162.5 mg (82%) is lower when compared to IR aspirin 81 mg (93%) following the first dose [Study NHP-ASA-001]. However, upon repeat administration of Asacard® 162.5 mg once-daily, near maximal inhibition of serum TxB_2 is achieved similar to what is achieved following repeat doses of IR aspirin 81 mg [Study CLICR-30].

(b) (4)

2.5.2 Is there a potential for a pharmacodynamic interaction between aspirin and ibuprofen? What are the instructions for use of DURLAZA with ibuprofen?

In 2006, FDA issued a drug safety communication[2] (DSC) alerting healthcare professionals about the potential for ibuprofen to attenuate the antiplatelet effect of low dose aspirin. The mechanism of interaction is possibly mediated via a competitive inhibition of the acetylation site on COX-1 for which aspirin is an irreversible inhibitor and ibuprofen, a reversible inhibitor. The presence of ibuprofen interferes with the binding of aspirin to COX-1, thereby attenuating the antiplatelet effect of aspirin. Although ibuprofen is a reversible inhibitor, the potential for interaction exists as aspirin is an irreversible platelet inhibitor with a short PK half-life (30 min to 1 h).

Attenuation of the antiplatelet effect of aspirin (as measured by serum TxB_2 and platelet aggregation assays) has been reported when a single-dose of ibuprofen 400 mg is administered within 30 min of administering IR aspirin or when ibuprofen is administered 8 h or less prior to IR aspirin dosing. However, as NHP-554C is a controlled release product of aspirin with a T_{max} in the range of 2 to 4 h in most subjects, it would be prudent to recommend administering ibuprofen after 2 to 4 h of NHP-554C administration. Therefore, in situations where twice-a-day dosing or more frequent dosing frequency for ibuprofen is warranted, this combination may not be possible to be used together.

Further, the DSC also recommends healthcare professionals to be aware of the possibility of other NSAIDs to interact with low dose aspirin unless it is proven otherwise.

[1] Stable hydrolysis metabolite of PGI_2 to assess the extent of preservation of PGI_2 biosynthesis

[2] Information for Healthcare Professionals: Concomitant Use of Ibuprofen and Aspirin. Link: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm

2.6 Biopharmaceutics

2.6.1 What is the effect of food on the bioavailability of the drug from the dosage form?

A high fat meal has been shown to further prolong the absorption of ASA from the drug product resulting in a delayed T_{max} (median = 4.0 h), modest increase in C_{max} (1.4-fold) and approx. 3-fold higher AUC, compared to when administered under fasted condition [Study ASA-001] [Fig. 4]. As a result of higher exposure to ASA in the presence of a high fat meal, the degree of inhibition of serum TxB_2 is also greater.

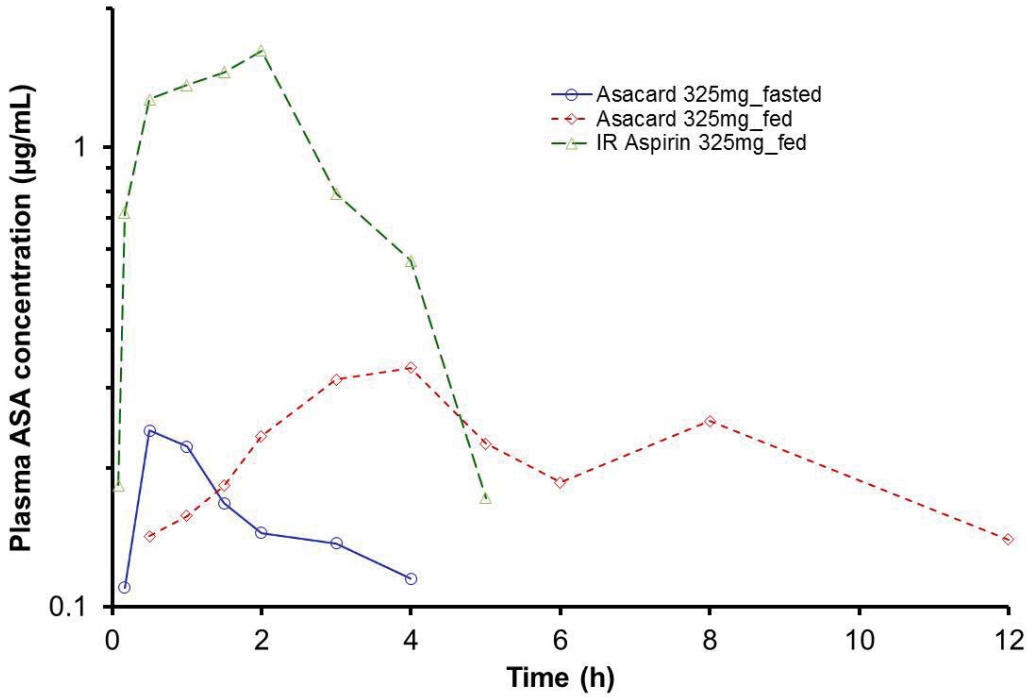

Figure 4: Mean plasma concentration-time course of ASA following administration of Asacard® 325 mg under fasted and fed condition, and IR aspirin 325 mg under fed condition [Study ASA-001].

However, these results have been obtained using Asacard® 325 mg and lacks an appropriate control arm i.e., IR aspirin 81 mg. Nevertheless, the results from study ASA-001 can be applied to study NHP-ASA-01 which evaluated the PK of ASA following both NHP-554C 162.5 mg and IR aspirin 81 mg (thereby, allowing a comparison within the same study). Using a 3-fold higher ASA exposure for NHP-554C 162.5 mg to account for the effect of food, the resulting exposures are approx. 2-fold higher when compared to IR aspirin 81 mg (fasted). It is known from the literature that IR aspirin does not have a positive food effect[3]. Though there is clinical experience for an increase in ASA exposure of this magnitude, the release characteristics of NHP-554C are altered. Therefore, DURLAZA should preferably be administered in a fasted state.

[3] Koch PA et al. J Pharm Sci. 1978 Nov; 67(11):1533-5

It is not known whether any type of food or only a high fat meal would increase systemic exposure to ASA from this drug product.

Table 3: Comparison of ASA exposures between study NHP-ASA-01 and ASA-001 to decipher the impact of food on NHP-554C relative to IR aspirin 81 mg

Plasma ASA	NHP-554C 162.5 mg (fasted)	NHP-554C 162.5 mg (fed)	IR aspirin 81 mg (fasted)
$AUC_{0\text{-}inf}$ (ng*h/mL)	917	2751†	1154

†applying a 3-fold higher exposure for the impact of food

2.6.2 What is effect of alcohol on the systemic bioavailability from the drug product? Are there any specific instructions on the use of alcohol with administration of this drug product?

Based on *in vitro* dissolution studies, greater than (b) (4)% of the drug is released within 1 h in a media containing 20% alcohol. When evaluated in a media containing 40% alcohol, almost (b) (4)% of the drug is released within (b) (4) min, indicative of a compromise in the controlled release micro-particle components in the presence of alcohol. Therefore, the product insert should include appropriate warning that avoids administration of this product with alcohol. For more details about *in vitro* alcohol dose dumping dissolution results, refer drug product review.

2.7 Bioanalytical Method Validation

Plasma concentration of ASA was measured by a validated LC-MS/MS assay in Study NHP-ASA-01. Concentration of TxB_2 (in serum) and 11-dehydro-TxB_2 (in urine) were measured by a validated enzyme-linked immunosorbent assay (ELISA). It was found that:

- The accuracy and precision values of at least two-thirds of the overall QC samples from the supporting bioanalytical reports were equal to or better than 15% (20% at the LLOQ).
- ASA, TxB_2 and 11-dehydro-TxB_2 samples were found to be stable in their respective media after 3 free/thaw cycles and after 6 h when placed in an ice-bath (ASA) or at room temperature (TxB_2 and 11-dehydro-TxB_2).
- Samples with concentration expected to be outside of the linear range were appropriately diluted prior to analysis. The QC sample accounting for dilution showed no bias.
- More than two-thirds of the incurred sample reanalysis (ISR) fell within 20% deviation.

The bioanalytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and is acceptable.

Note: Bioanalysis of ASA, SA, TxB_2 and 11-dehydro-TxB_2 from Study NHP-ASA-01 were performed at (b) (4) As PD (primary) and PK (secondary) results from Study NHP-ASA-01 was critical to this NDA supporting a regulatory

action, OCP requested an inspection of the bioanalytical site via Office of Scientific Investigations (OSI) on 12/10/2014. The results of the inspection are pending at the time of this review and as such the proposed recommendations are not final.

3. INDIVIDUAL STUDY REVIEWS

3.1 Dose-response

Dose-response		
Study report: NHP-ASP-01	**Study period:** 04/2013 - 07/2013	EDR Link[4]
RATIONALE		
This study was performed so as to choose a dose of NHP-55C that is pharmacodynamically equivalent to IR aspirin 81 mg. Therapeutic equivalence based on bioequivalence of PK measures was not pursued, as NHP-554C was expected to have a sustained release of ASA resulting in low systemic exposures when compared to IR aspirin but with adequate levels in the portal vein so as to result in similar PD effects. Hence, the Division envisioned a dose-response study with comparison of ED_{50s} between NHP-554C and IR aspirin towards PD markers of importance to aspirin (serum TxB_2, 11-urinary dehydro-TxB_2 and platelet aggregation) to aid in deriving a dose of NHP-554C that would be therapeutically equivalent to IR aspirin 81 mg. As repeat dose administration and doses higher than 81 mg were going to decrease the ability to demonstrate dose-response and discriminate between the two products, the Division recommended the study to be performed at doses less than 81 mg and following a single-dose.		
OBJECTIVE		
i. To characterize the dose-pharmacodynamic response relationship of NHP-554C (controlled release aspirin) compared to IR aspirin following a single-dose in healthy subjects ii. To characterize pharmacokinetics of NHP-554C		
STUDY DESIGN		
Single center, open label, 4-way, randomized, crossover, single-dose, dose-response study. Treatments were separated by a wash-out period of at least 14 days. *NHP-554C*: 20, 40, 81, 162.5 and 325 mg *IR aspirin*: 5, 10, 20, 40 and 81 mg The doses for IR aspirin were selected so as to provide between 10% and near maximal inhibition of serum TxB_2 and urinary 11-dehydro-TxB_2 following the first dose. NHP-554C doses were selected with an expectation that the respective dose levels would provide a similar PD effect after a single dose as those observed for IR aspirin. A range of doses for NHP-554C was generated by varying the amount of micro-particles in a capsule. To generate lower doses of the reference product, IR aspirin was ground up and then the desired amounts placed in capsules. Subjects were randomly assigned to receive two of NHP-554C doses and two of IR aspirin doses with no two same formulation type administered in consecutive periods. Subjects remained domiciled in the clinical research unit through completion of day 2 procedures of each period (approx. 24 h post-dosing). Period 4, day 2 served as the end-of-study visit.		
Population		
Healthy male and female subjects (aged 18 to 55 years) Fifty subjects were to be enrolled in the study, with a goal of completing approx. 18 subjects for each treatment. A sample size of 15 subjects was determined to permit the characterization of the mean		

[4] \\Cdsesub1\evsprod\NDA200671\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\nhp-asp-01\nhp-asp-01-body.pdf

area under the effect-time curve (AUEC) over the 24 h period after administration of NHP-554C with a relative standard error of 20%.

PK Sampling

Blood samples for ASA and SA determination were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 4, 8, 16 and 24 h post-dose.

PD Sampling

Blood samples for serum TxB_2 determination and platelet aggregation analyses were collected pre-dose and at 0.5, 1, 2, 4, 8, 16 and 24 h post-dose. Platelet aggregation in response to aspirin using arachidonic acid and collagen as agonist was measured using light transmission aggregometry.

Urine samples for 11-dehydro-TxB_2 and creatinine determination were collected pre-dose and during the following periods: 0-8, 8-16 and 16-24 h post-dose.

Statistical methods

PK: Descriptive statistics for PK measures; *PD*: Primary PD parameter ED_{50} for serum TxB_2, urinary 11-dehydro-TxB_2 and platelet aggregation was derived using an E_{max} model (WinNonlin v5.3).

RESULTS

Bioanalysis assay method

	ASA	SA
Method	**LC-MS/MS**	**LC-MS/MS**
LLOQ (ng/mL)	10	40
Range (ng/mL)	10 – 6,000	40 – 12,000
QCs (ng/mL)	30, 945, 4726	117, 1873, 9365

	Serum TxB_2	11-dehydro-TxB_2
Method	**ELISA**	**ELISA**
LLOQ (pg/mL)	7.80	31.3
Range (pg/mL)	7.80 – 700	31.3 – 1,400
QCs (pg/mL)	20, 200, 550	45, 400, 1100

Comment: The analytical assay method for PK and PD measures are acceptable since the accuracy and precision of two-thirds of the QC and LLOQ samples are within ±15% and ±20%, respectively. More than two-thirds of the incurred sample reanalysis fall within 20% deviation.

Subject disposition and analysis datasets

Overall study: Three subjects discontinued the study early (Table 1). One subject discontinued due to an AE (NHP-554C 20 mg) and two due to protocol violation for testing positive for amphetamines and barbiturates, respectively (IR aspirin 10 and 20 mg).

Table 1: Subject disposition in NHP-ASP-01

Subjects	NHP-554C, mg					IR aspirin, mg				
	20	**40**	**81**	**162.5**	**325**	**5**	**10**	**20**	**40**	**81**
Exposed	20	19	18	18	20	20	19	20	20	18
Completed	19	19	18	18	20	20	18	19	20	18

PK analyses dataset: Included all randomized subjects who received at least one dose of study medication and who had any plasma concentration data.

PD analyses dataset: Included all randomized subjects who received at least one dose of study medication and who had at least one PD result post-dose. Due to unusually high or low baseline values in PD measures (serum TxB_2 and urinary-11-dehydro-TxB_2) observed in a few subjects, subjects with baseline values greater than 97.5th percentile and lower than 2.5th percentile were excluded from the respective PD analysis datasets.

Pharmacokinetics

Note: The review lists and discusses the results of ASA PK only, as ASA is the moiety of interest pertinent to cardiovascular indication. For SA PK results, please refer NHP-ASP-01 clinical study report.

- Time to reach peak ASA concentration (T_{max}) is slightly delayed (by 0.5 - 1 h) following NHP-554C administration when compared to IR aspirin.
- The relative bioavailability of ASA following NHP-554C administration is approx. 37% when compared to IR aspirin (ratio of $AUC_{0\text{-last}}$ geometric means between NHP-554C 81 mg and IR aspirin 81 mg). The C_{max} of ASA following NHP-554C administration is approx. 21% to that of IR aspirin.
- Systemic ASA concentrations are prolonged following NHP-554C in comparison to IR aspirin.
- Due to sustained absorption of ASA from NHP-554C, the mean half-life ($t_{1/2}$) following NHP-554C administration is slightly prolonged (approx. 2 h) when compared to IR aspirin (45-60 min) administration.

Table 1a: Summary of ASA PK measures across NHP-554C treatment groups

NHP-554C dose (mg)	T_{max} (min)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng*h/mL)	$t_{1/2}$ (h)
20	2.0 [0.5 – 8.0]	20 [45]	38.4 [93]	--
40*	2.0 [1.0 – 8.0]	40.1 [27]	129 [59]	--
81†	4.0 [1.5 – 4.0]	114 [42]	343 [35]	--
162.5†	1.75 [0.5 – 8.0]	179 [26]	649 [37]	2.0 [23]
325	2.0 [1.0 – 4.0]	418 [29]	1630 [30]	1.9 [21]

Table 1b: Summary of ASA PK measures across IR aspirin treatment groups

IR aspirin dose (mg)	T_{max} (min)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng*h/mL)	$t_{1/2}$ (h)
5	1.0 [0.5 – 4.0]	26.5 [35]	28.4 [34]	--
10*	2.0 [0.5 – 4.0]	69.4 [40]	80.2 [37]	--
20	1.5 [1.0 – 2.0]	126 [23]	158 [38]	--
40	1.5 [1.0 – 4.0]	240 [31]	400 [28]	0.90 [40]
81†	1.5 [0.5 – 2.0]	521 [26]	893 [23]	0.63 [41]

Data expressed as arithmetic mean [CV%]; For T_{max} data expressed as median [min – max]

* N=19; † N=18; -- Cannot be calculated reliably

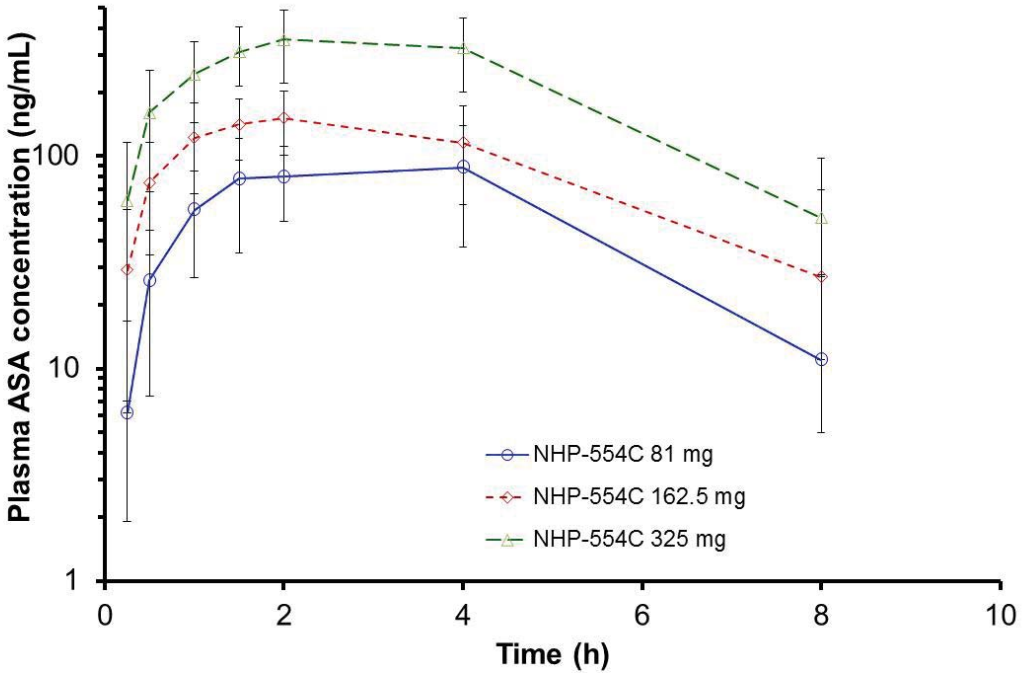

Figure 1a: Mean plasma concentration-time course of ASA across NHP-554C dose groups (highest 3 dose groups shown). Data expressed as mean ± SD.

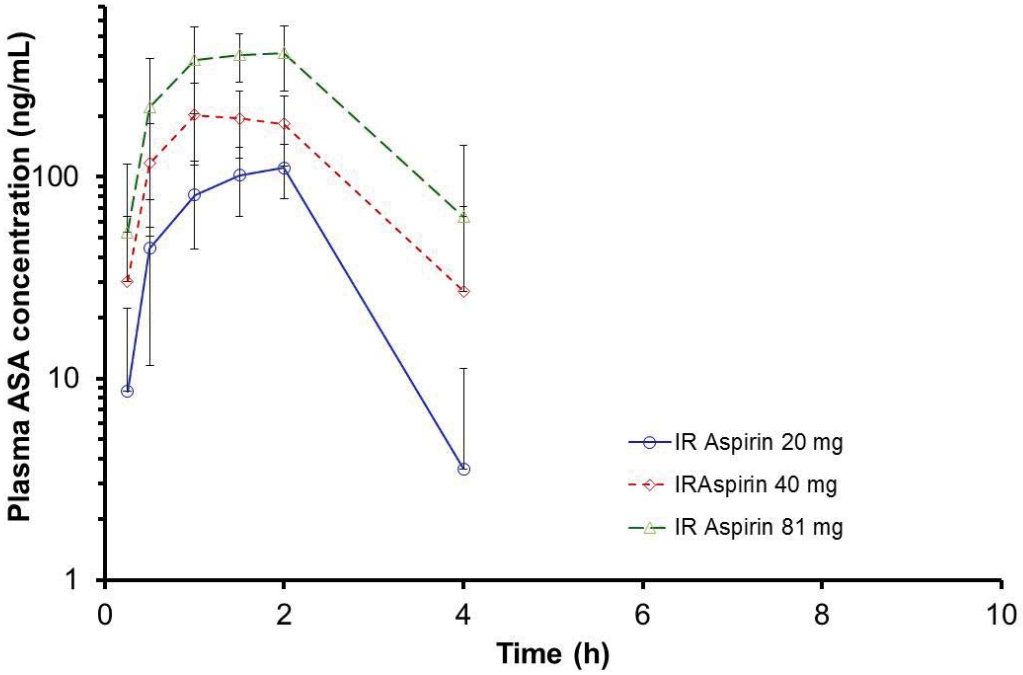

Figure 1b: Mean plasma concentration-time course of ASA across IR aspirin dose groups (highest 3 dose groups shown). Data expressed as mean ± SD.

Pharmacodynamics

Serum-TxB_2

The response variable (E) used was inhibition of serum TxB_2 calculated for each subject as shown in Eqn. 1

[(Value at baseline – Value at 24 h post-dose) / Value at baseline] x 100 ------ Eqn. 1

The primary PD parameter, ED_{50} i.e., dose that results in 50% of the maximal effect (E_{max}), was derived using a sigmoid E_{max} model (best suited) as shown in Eqn. 2.

$E = (E_{max} * D^{\gamma}) / (D^{\gamma} + ID_{50}^{\gamma})$ ------ Eqn. 2

where, γ represents the slope factor.

Graphical representation of observed data with E_{max} model fit is shown in Fig. 2. The PD parameters are shown in Table 2. Time course of observed serum TxB_2 inhibition following NHP-554C 162.5 mg and IR aspirin 81 mg is shown in Fig. 3.

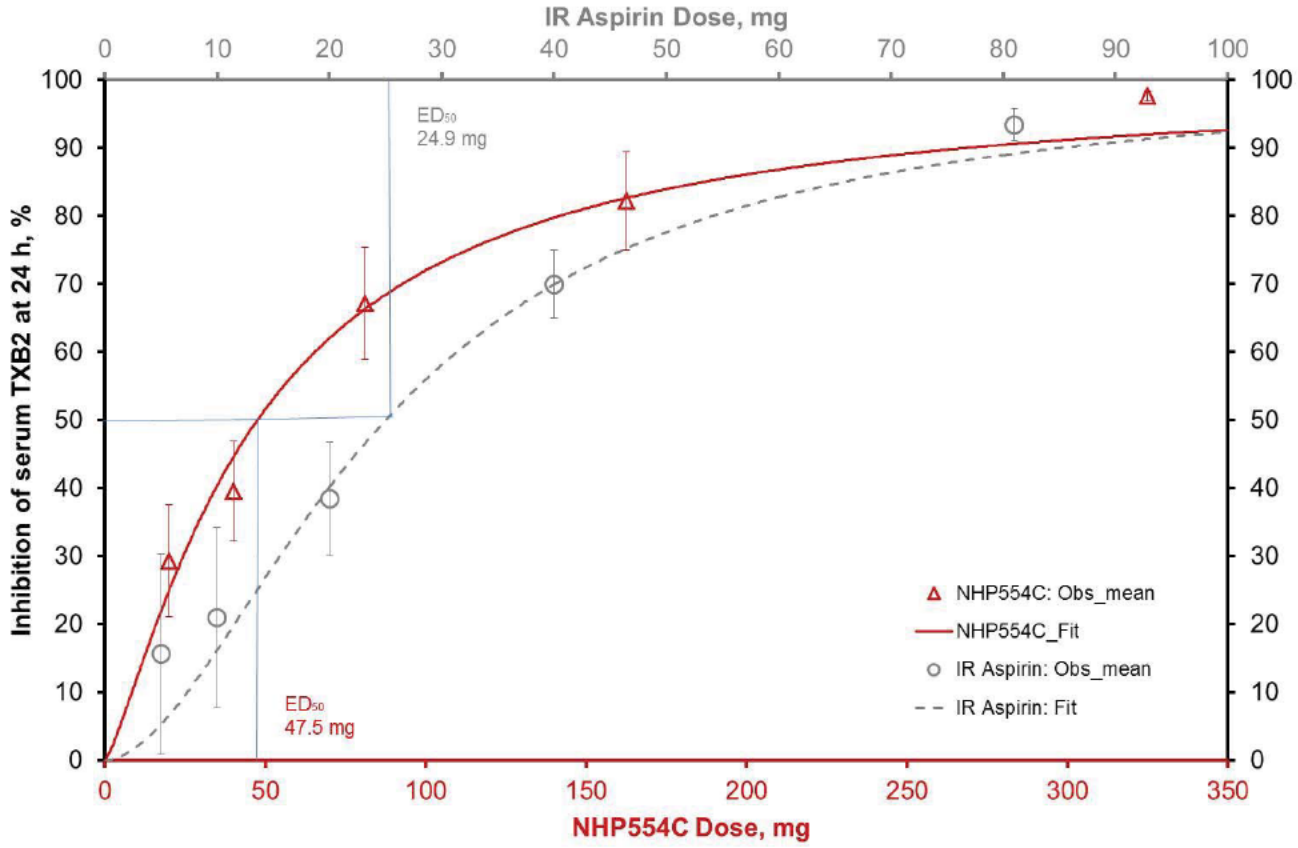

Figure 2: Inhibition of serum TxB_2 at 24 h post-dose following a single dose administration of NHP-554C (20, 40, 81, 162.5, or 325 mg) or IR aspirin (5, 10, 20, 40, or 81 mg). The plot is color coded to differentiate between NHP-554C (red) and IR aspirin (gray) treatment arms. The observed response variable is shown as mean ± SE, as represented by open triangles and circles (± error bars) for NHP-554C and IR aspirin, respectively. The sigmoid E_{max} model fit through the subject level data is represented by the red solid and gray broken lines for NHP-554C and IR aspirin, respectively.

Table 2: PD parameters for inhibition of serum TxB_2 between treatment groups. Data expressed as mean [CV%]

Serum TxB_2	IR aspirin	NHP-554C
E_{max}, %	99.9 [24.7]	99.9 [17.6]
ED_{50}, mg	24.9 [40.1]	47.5 [37.6]
Gamma (γ)	1.79 [44.9]	1.26 [38.0]

CV% expressed in parenthesis

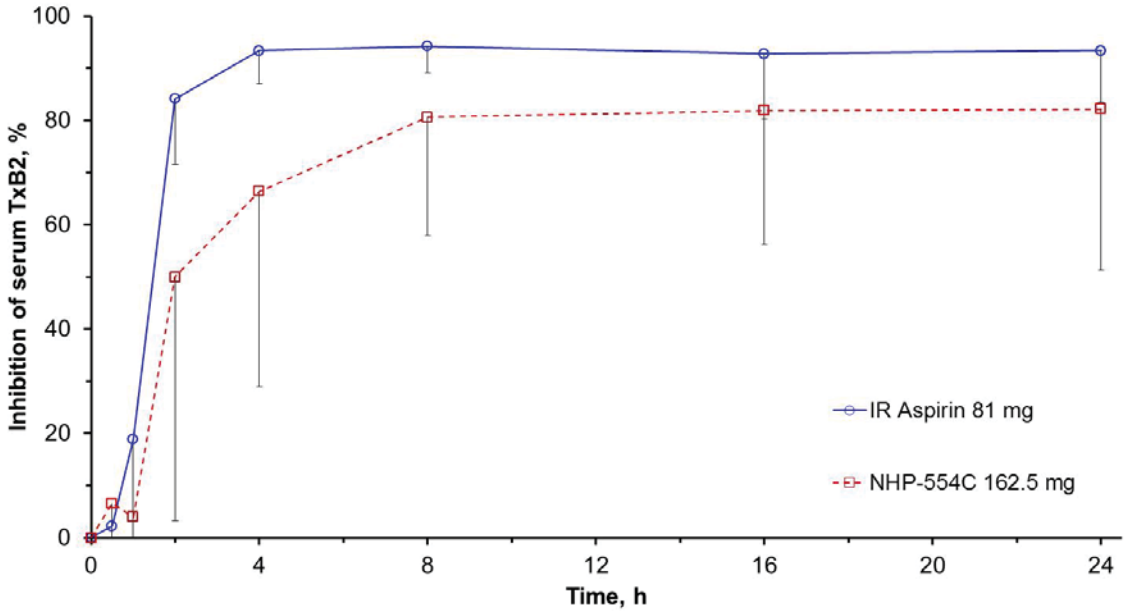

Figure 3: Time course of inhibition of serum TxB_2 following NHP-554C 162.5 mg and IR aspirin 81 mg up to 24 h post-dose. Data points represent mean; error bars represent SD.

Urinary 11-dehydro-TxB_2

The response variable used was inhibition of urinary 11-dehydro-TxB_2 corrected for creatinine calculated for each subject as shown in Eqn. 1. The primary parameter ED_{50} was derived using a sigmoid E_{max} model (best suited) as shown in Eqn. 2. Graphical representation of observed data with E_{max} model fit is shown in Fig. 4. The PD parameters are shown in Table 3.

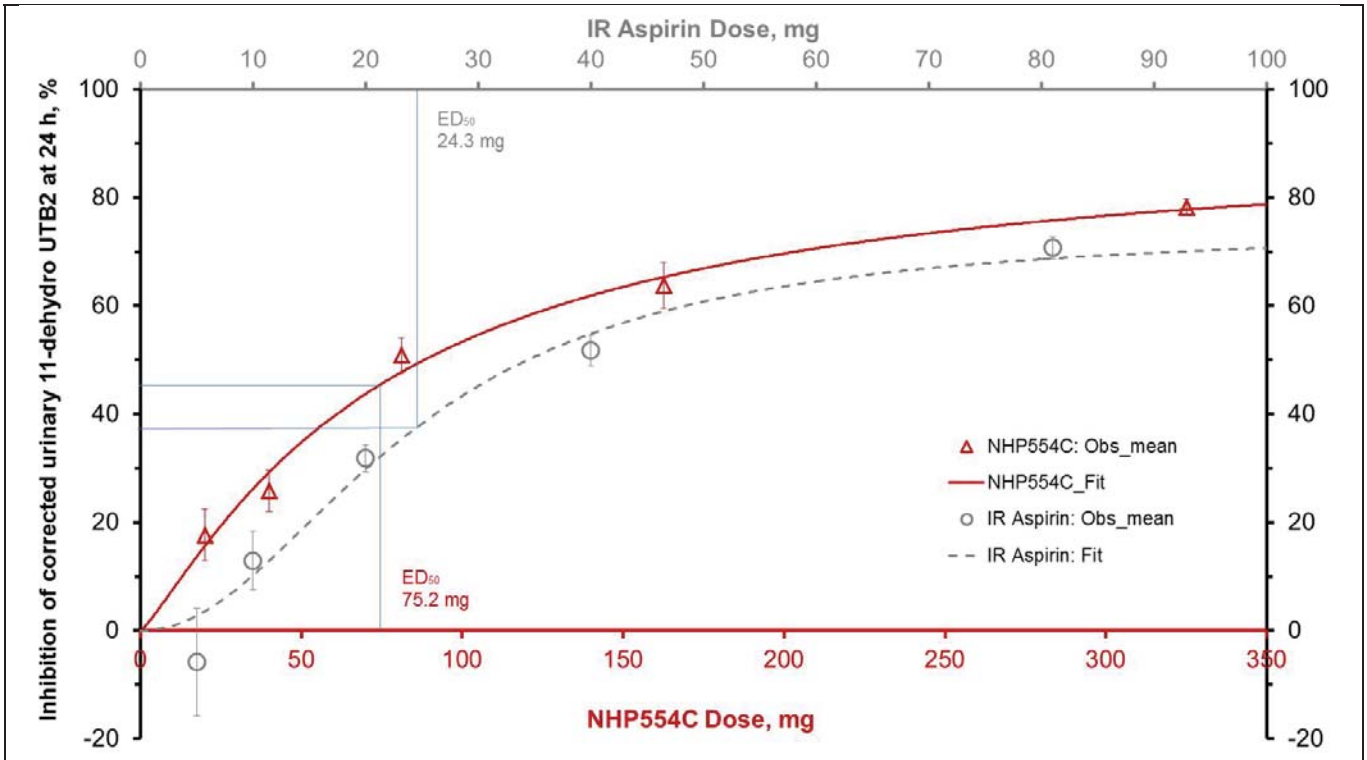

Figure 4: Inhibition of corrected urinary 11-dehydro-TxB_2 at 24 h post-dose following a single dose administration of NHP-554C (20, 40, 81, 162.5, or 325 mg) or IR aspirin (5, 10, 20, 40, or 81 mg). The plot is color coded to differentiate between NHP-554C (red) and IR aspirin (gray) treatment arms. The observed response variable is shown as mean ± SE, as represented by open triangles and circles (± error bars) for NHP-554C and IR aspirin, respectively. The sigmoid E_{max} model fit through the subject level data is represented by the red solid and gray broken lines for NHP-554C and IR aspirin, respectively.

Table 3: PD parameters for inhibition of urinary 11-dehydro TxB_2 between treatment groups. Data expressed as mean [CV%]

Urinary 11-dehydro-TxB_2	**IR aspirin**	**NHP-554C**
E_{max}, %	90.0 [25.8]	91.2 [13.9]
ED_{50}, mg	32.6 [41.6]	75.2 [30.5]
Gamma (γ)	1.61 [34.1]	1.19 [22.2]

CV% expressed in parenthesis

Platelet aggregation inhibition

- There was no inhibition of platelet aggregation in response to aspirin when collagen was used as agonist. This may be expected as aspirin specifically inhibits arachidonic acid mediated platelet aggregation.
- Inhibition of platelet aggregation in response to aspirin using arachidonic acid as agonist was highly variable, particularly NHP-554C 162.5 mg and IR aspirin 81 mg dose groups (Fig. 5A and 5B). Due

to highly variable results in these dose groups, no further analyses of the data were conducted.

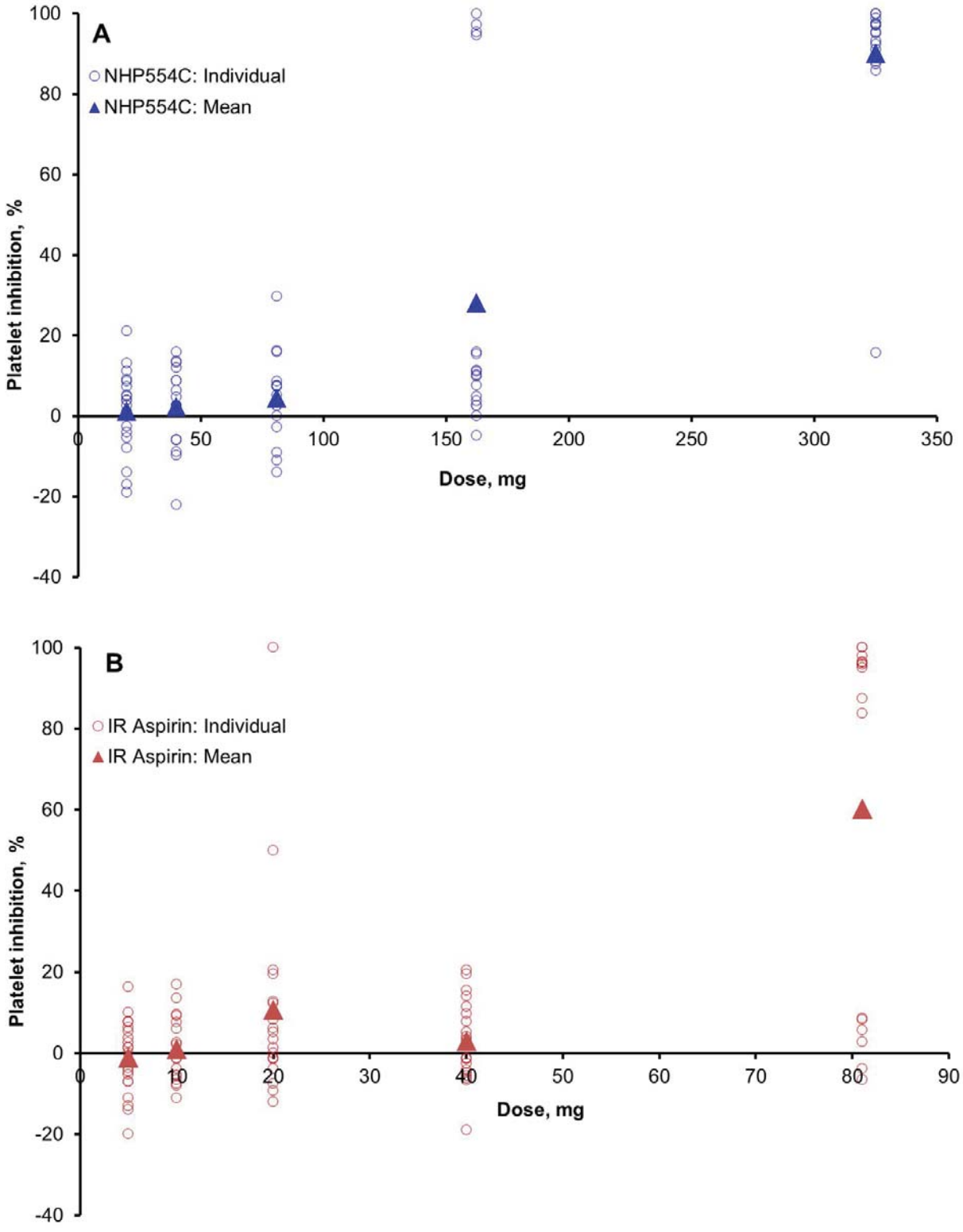

Figure 5: Inhibition of platelet aggregation results (subject level and mean) across (A) NHP-554C, and

(B) IR aspirin dose groups using arachidonic acid as agonist.
Safety
No death/SAE
CONCLUSION
• The ED_{50} for inhibition of serum TxB_2 and urinary 11-dehydro-TxB_2 is 1.9-fold and 2.3-fold higher for NHP-554C when compared to IR-aspirin. Therefore, using a 2-fold difference in ED_{50} values between NHP-554C and IR aspirin, the pharmacodynamic effects attained following IR aspirin 81 mg should be obtained with NHP-554C 162.5 mg. • Based on observed data, the mean serum TxB_2 inhibition following NHP-554C 162.5 mg (mean ± SD: 82.2% ± 31) is lower following the first dose when compared to that following IR aspirin 81 mg (93.4% ± 10). However, upon repeat doses of NHP-554C 162.5 mg near maximal inhibition of serum TxB_2 effects should be obtained.

3.2 Food Effect

Food Effect		
Study report: ASA-001	**Study period:** 08/1997 - 11/1997	EDR Link[5]
OBJECTIVE		
i. To evaluate the impact of food on the PK and PD (degree of serum TxB_2 inhibition) of ASA following administration of Asacard® 325 mg under fed and fasted conditions in healthy subjects ii. To compare the PK and PD (degree of serum TxB_2 inhibition) of ASA following a single-dose of Asacard® and Bayer® aspirin (immediate release) at 325 mg when administered under fed condition in healthy subjects		
STUDY DESIGN		
Single center, open label, randomized, single-dose, three treatment, three period, six sequence crossover study. Treatments were separated by a wash-out period of at least 14 days. *Treatment A*: 325 mg Asacard®, fasted (following overnight fast of at least 10 h) *Treatment B*: 325 mg Asacard®, fed (standardized high-fat meal 30 min prior to drug administration) *Treatment C*: 325 mg Bayer® immediate release aspirin, fed (standardized high-fat meal 30 min prior to drug administration)		
Population		
Healthy male subjects (aged 18 to 40 years) *Enrolled*: N = 26; *Completed*: N = 24 (2 subjects discontinued early due to non-compliance)		
PK Sampling		
Blood samples for ASA and SA determination were collected pre-dose and at 5, 10, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72 and 96 h post-dose.		
PD Sampling		
Blood samples for serum TxB_2 determination were collected pre-dose and at 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 144 and 240 h post-dose. Urine samples for 6-keto-prostaglandin $F_1\alpha$ were collected pre-dose and during the following time periods: 0-6, 6-12 and 12-24 h post-dose.		
Statistical method		
PK: (i) Descriptive statistics, (ii) A mixed-effect ANOVA model on log transformed C_{max} and AUC was fitted with sequence, period, treatment and subjects within sequence as factors. Two-sided 90% CIs for the GMR of the PK measure between different treatment groups was calculated.		

[5] \\Cdsesub1\evsprod\NDA200671\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\asa-001\asa-001-pk-report.pdf

RESULTS

Bioanalysis assay method

	Serum TxB_2
Method	**ELISA**
LLOQ (pg/mL)	100
Range (pg/mL)	100 - 10000
QCs (pg/mL)	100, 200, 300, 600, 1200

Comment: The analytical assay method for serum TxB_2 is acceptable since the accuracy and precision of two-thirds of the QC and LLOQ samples are within ±15% and ±20%, respectively. Also, more than two-thirds of the incurred sample reanalysis fall within 20% deviation. Bioanalytical method validation for ASA is not available.

Pharmacokinetics

- Absorption of ASA following administration of NHP-554C with a high fat meal is slower and prolonged relative to when administered in a fasted state. The time to reach peak concentration (T_{max}) is delayed by 2 - 3 h in the presence of food (Table 1).

- There is a modest increase in C_{max} of ASA in the presence of a high fat meal (Table 2). The prolonged absorption of ASA in the presence of a high fat meal increases the AUC by approx. 3-fold for Asacard® (Table 2).

- The relative bioavailability of Asacard® in comparison to IR aspirin under fed conditions is approx. 42%. The C_{max} of ASA following administration of Asacard® is approx. 15% to that of IR aspirin under fed conditions (Table 2).

Note: SA PK results are not discussed as it is not the active moiety pertinent to the CV indication that the applicant seeks.

Table 1: Summary of ASA PK measures across treatment groups

PK Measure	Mean [CV%]		
	Treatment A Asacard® fasted N = 24	**Treatment B** Asacard® fed N = 24	**Treatment C** IR aspirin fed N = 24
T_{max} (h)	0.5 [0.5 – 2.0]	4.0 [1.5 – 8.0]	1.5 [0.5 – 3.0]
C_{max} (µg/mL)	0.265† [30]	0.381† [36]	2.54 [47]
AUC_{0-t} (µg*h/mL)	0.446† [49]	1.425† [42]	3.99 [20]
AUC_{0-inf} (µg*h/mL)	0.683‡ [35]	1.928‡ [32]	4.34ᵞ [19]
$t_{1/2}$ (h)	1.12‡ [41]	1.64‡ [33]	0.526ᵞ [41]

T_{max} reported as median [range]
† N = 23; ‡ N = 19; ᵞ N = 20

Table 2: Relative bioavailability between treatment groups

PK Measure	Treatment	N	LS Mean	Comparison	GMR	90% CI
C_{max}	A	23	0.253	A vs B	1.42	1.18 – 1.71
	B	23	0.358			
	C	24	2.31	B vs C	6.44	5.36 – 7.74
AUC_{0-t}	A	23	0.386	A vs B	3.31	2.69 – 4.08
	B	23	1.28			
	C	24	3.91	B vs C	3.07	2.49 – 3.77
AUC_{0-inf}	A	19	0.616	A vs B	2.94	2.51 – 3.44
	B	19	1.81			
	C	20	4.28	B vs C	2.36	2.02 – 2.76

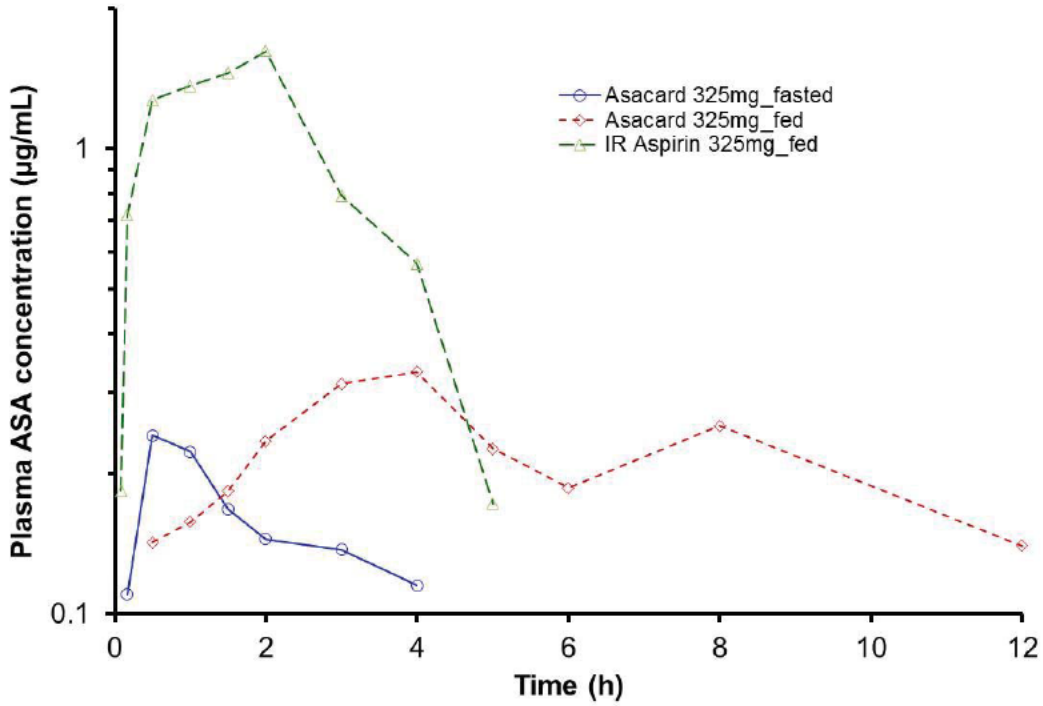

Figure 1: Mean plasma concentration-time course of ASA across treatment groups.

Pharmacodynamics

- Inhibition of serum TxB_2 was highest in the IR aspirin fed treatment arm (>99%) followed by Asacard® fed (approx. 96%) and Asacard® fasted (approx. 75%) treatment arms. The peak inhibition is manifested earlier with IR aspirin when compared to that of Asacard® treatment arms.

- The results for 6-keto-prostaglandin $F_1\alpha$ have not been described in the study report and no conclusions are made specific to 6-keto-prostaglandin $F_1\alpha$.

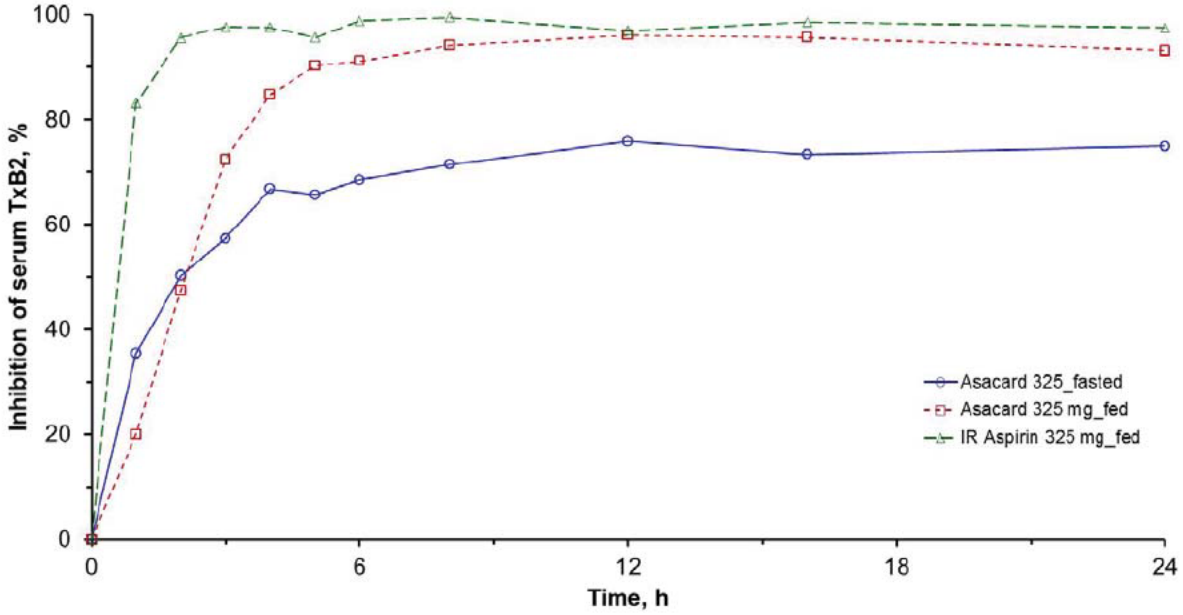

Figure 2: Time course (up to 24 h post-dose) of mean serum TxB_2 inhibition across treatment groups.

Safety
No death/SAE
CONCLUSION
A high fat meal delays and prolongs the absorption of ASA from Asacard®. There is a modest increase in C_{max} (40% ↑), delay in T_{max} (median 4.0 h) and increase in AUC of approx. 3-fold when Asacard® is administered with a high fat meal relative to when administered under fasted condition.

3.3 Effect on vascular prostaglandins and thromboxane synthesis

Effect on vascular prostaglandins and thromboxane synthesis

Study report: CLICR 30	**Study period:** 04/1994 - 02/1995	EDR Link[6]

OBJECTIVE

To compare vascular prostaglandins and thromboxane synthesis following repeat administration of Asacard® 162.5 mg (controlled release aspirin) and Kardegic® 160 mg (immediate release aspirin) for 10 days in healthy subjects

STUDY DESIGN

Single center, open label, randomized, two treatment, two period crossover study. Treatments were separated by a wash-out period of at least 14 days.

Treatment A: 162.5 mg Asacard® once-daily for 10 days
Treatment B: 162 mg Kardegic® (powder in sachet) once-daily for 10 days

Note: Kardegic® is an European approved OTC product of immediate release aspirin

Population

Healthy male subjects (aged 18 to 40 years)

Enrolled: N = 12; *Completed*: N = 12 (no drop-outs)

PK Sampling

Blood samples for ASA and SA determination were collected pre-dose and at 5, 10, 15, 30 min, 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 h post-dose on days 1 and 5.

PD Sampling

Blood samples for serum TxB_2 determination were collected pre-dose and at 24 h post-dose on days 1, 4, 7 and 10. An additional sample was collected 10 days after the end of second period.

Urine samples for 11-dehydro-TxB_2 and dinor-6-keto-F1α were collected pre-dose and at following time periods: 0-4, 4-8, 8-16, 16-24, 24-32, 32-40, 40-48, 89-96, 234-240 h post-first dose.

Statistical method

PK and PD: Descriptive statistics

RESULTS

Bioanalysis assay method

	ASA
Method	**HPLC-UV**
LLOQ (µg/mL)	0.100
Range (µg/mL)	0.25 – 2.5
QCs (µg/mL)	0.75, 1.25, 2.00

Comment: The analytical assay method is acceptable since the accuracy and precision of two-thirds of the QC and LLOQ samples are within ±15% and ±20%, respectively. The bioanalytical assay method validation for serum TxB_2, 11-dehydro-TxB_2 and dinor-6-keto-F1α are not available.

[6] \\Cdsesub1\evsprod\NDA200671\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\clicr-30\clicr-30.pdf

Pharmacokinetics

Note: Following administration of Asacard®, plasma concentrations of ASA were not detectable in 3 subjects on day 1 and 5 subjects on day 5. In rest of the subjects, the plasma concentrations were only transiently detectable (1 or 2 time points) at low concentrations (usually <0.2 µg/mL). The transience or absence of plasma concentrations per individual limits calculation of PK measures for any meaningful interpretation.

SA PK results are not discussed, as it is not the active moiety pertinent to the CV indication that the applicant seeks.

Pharmacodynamics

Serum TxB_2

- Inhibition of serum TxB_2 following the first dose (day 1: 24 h post-dose) is lower following administration of Asacard® 162.5 mg (mean: 64%) when compared to Kardegic® 160 mg (mean: 97%) (Fig. 1).

- Upon repeat dosing of Asacard® 162.5 mg, the inhibition of serum TxB_2 reaches near maximal values (mean: 95%) as observed on day 4 (earliest observation post day 1). The mean inhibition of serum TxB_2 following repeat administration of Kardegic® 160 mg ranges from 97% to 99% (Fig. 1).

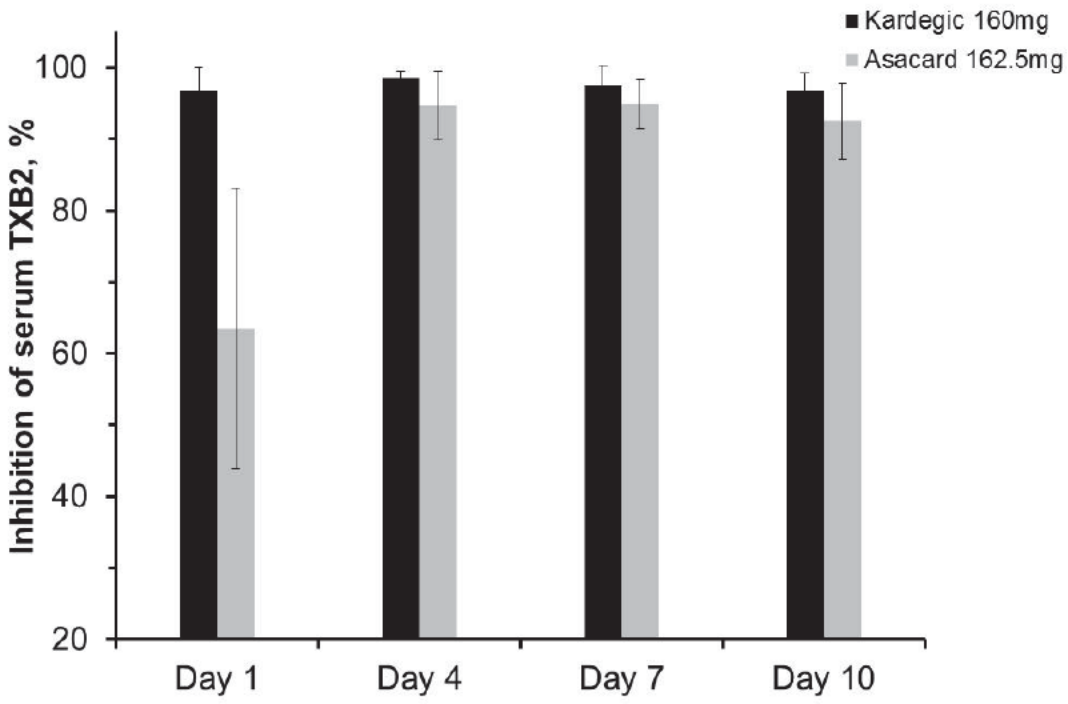

Figure 1: Inhibition of serum TxB_2 following multiple doses of Kardegic® 160 mg and Asacard® 162.5 mg. Data expressed as mean ± SD.

Urinary 11-dehydro-TxB_2

The mean inhibition of urinary 11-dehydro-TxB_2 is numerically lower following the first dose and marginally increases upon repeat doses for both treatments. However, not much credence should be given to these results due to high variability (Fig. 2).

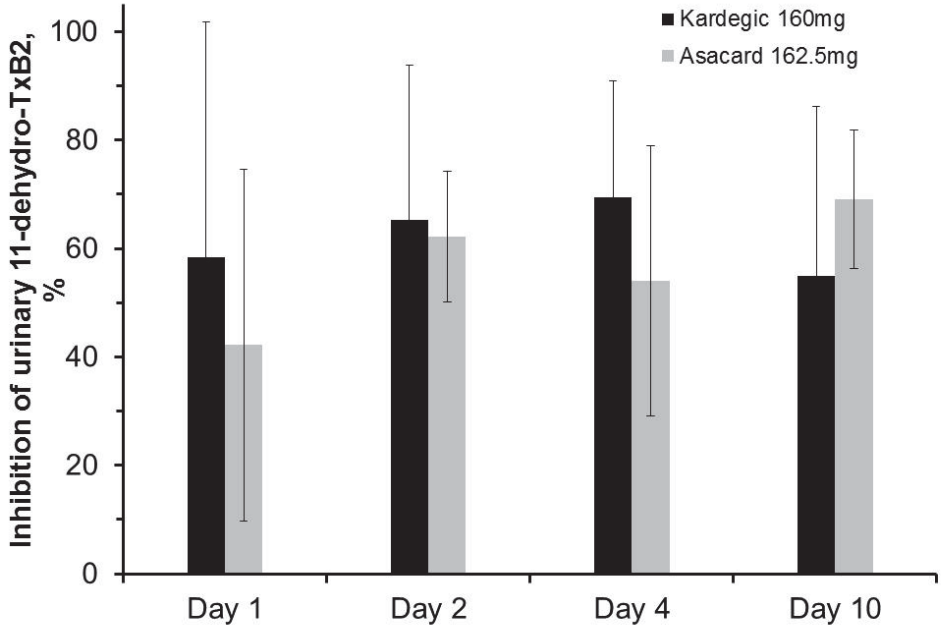

Figure 2: Inhibition of urinary 11-dehydro-TxB_2 following multiple doses of Kardegic® 160 mg and Asacard® 162.5 mg. Data expressed as mean ± SD.

Urinary 6-keto-PGF1α

There is no difference in the levels of 6-keto-PGF1α between both treatments taking into account the values at baseline (Fig. 3).

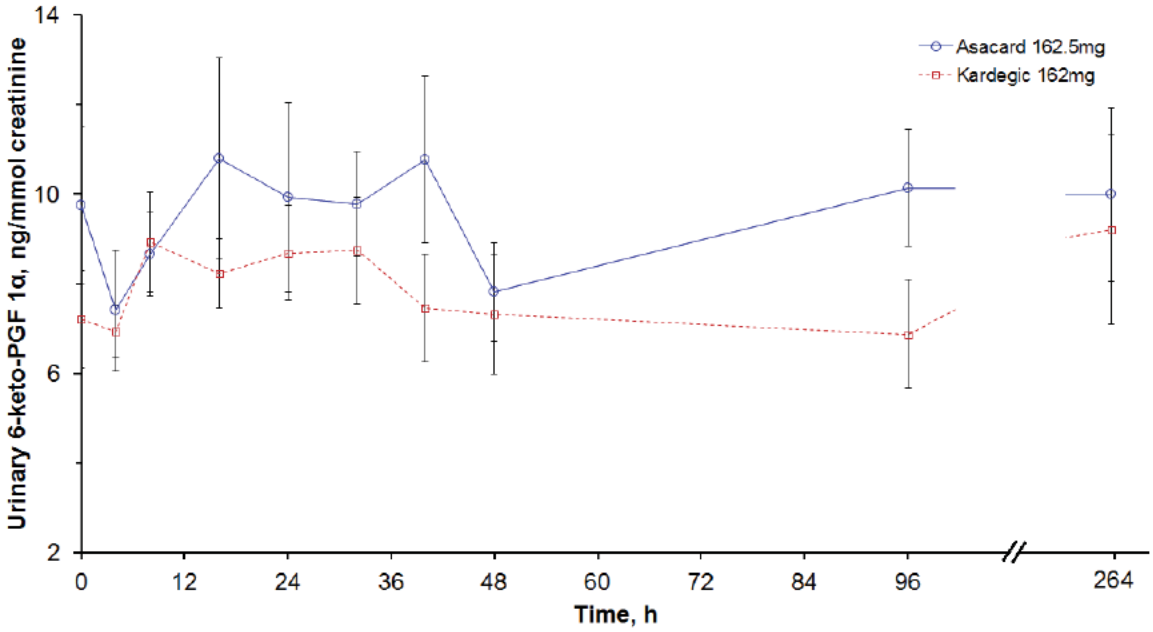

Figure 3: Urinary 6-keto-PGF1α levels (corrected for creatinine) following administration of Asacard® 162.5 mg and Kardegic® 160 mg. Data expressed as mean ± SD.

Safety
No death/SAE
CONCLUSION
Inhibition of serum TxB_2 following the first dose of Asacard® 162.5 mg is lower in comparison to the first dose of Kardegic® 160 mg. However, upon repeat doses of Asacard® 162.5 mg, inhibition of serum TxB_2 reach near maximal values similar to that observed with repeat doses of Kardegic® 160 mg. (b) (4) (b) (4)

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/s/

SUDHARSHAN HARIHARAN
06/01/2015

RAJANIKANTH MADABUSHI
06/02/2015

BIOPHARMACEUTICS NDA REVIEW
Office of New Drugs Products
Division of Biopharmaceutics

Application No.:	NDA 200671	**Reviewer:** Sandra Suarez Sharp, PhD and Kimberly Raines, PhD	
Submission Date:	September 5, 2014 January 30, 2015 March 25, 2015 March 27, 2015 April 28, 2015		
Division:	Division of Cardiovascular and Renal Products (DCRP)	**Branch Chief (acting):** Angelica Dorantes, Ph.D.	
Sponsor:	New Haven Pharmaceuticals	**Biopharmaceutics Director (Acting):** Paul Seo, PhD	
Trade Name:	DURLAZA	**Date Assigned:**	Sep 14, 2014
Generic Name:	Controlled Release Acetylsalicylic acid (ASA) microparticles in a capsule	**Date of Review:**	April 30, 2015
Indication:	Secondary prevention of cardiovascular (CV) events	**Type of Submission:** New Drug Application 505(b)(2)	
Formulation/ strengths	ER Capsules; 162.5 mg		
Route of Administration	Oral		

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

This submission is a 505(b)(2) application for a controlled release Acetylsalicylic acid (ASA) indicated for the once daily secondary prevention of acute cardiovascular events.

DURLAZA, NHP-554C, Extended Release Capsules (b) (4) consist of ASA microcapsules, (b) (4). The ASA microcapsules are composed of an ASA drug substance core which has been (b) (4) (b) (4) the drug substance is performed to achieve the extended release dissolution profile of the drug product. A 'loading dose' of approximately (b) (4)% of the total dose is delivered within the first three hours followed by sustained release for the remainder of the 24 hour period primarily through diffusion. ASA drug substance in a particle-size range of (b) (4) was selected because of its compatibility with the (b) (4) process and the intended release profile.

This review focuses on: a) the acceptability of the dissolution method and acceptance criteria; b) the extended release designation claim; c) the in vitro dose dumping in the presence of alcohol and; d) bridging across phases of formulation development. The bridging supporting the 505(b)(2) submission relies on PK/PD studies being reviewed by OCP.

a) Dissolution Method and Acceptance Criteria:
The dissolution medium selected was phosphate buffer pH 7.4 containing sodium azide and (b) (4)% trypsin, an endogenous, intestinal enzyme that (b) (4) mimics the conditions encountered in the jejunum and ileum where the microcapsules are distributed. The following acceptance criteria was recommended by the FDA and accepted by the Applicant on April 28, 2015.

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
ASA	ER Capsule	II (paddle)	100	0.05M Potassium Phosphate Buffer (pH 7.4) with trypsin and sodium azide with spiral sinker	900 mL, 37 °C	1 hour: (b) (4)% 3 hour: % 9 hour: % 22 hour: % 30 hour: N (b) (4)%

(b) (4)

b) The Extended-Release Designation Claim
The following data were provided to support the extended release designation claim:

1. The drug product's steady-state performance is comparable (the degree of fluctuation in the PK parameters was lower) to a currently marketed non-controlled release drug product that contains the same active drug ingredient that is subject to an approved NDA (UPSA® aspirin hard gelatin capsule 325 mg). Refer also to ClinPharm review for information related to bioequivalent PK/PD performance in comparison to the reference drug;
2. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;
3. The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product;

Data from multiple dose Study PKFT97.1 demonstrated that the salicylic acid plasma concentration-time curves following multiple daily administration have a smoother PK profile (e.g., lower Cmax and similar Cmin) with a decreased fluctuation index at steady-state plasma

concentrations as compared to UPSA aspirin hard gelatin capsules. In addition, the %CV values for the relevant PK parameters of the proposed drug product are comparable and in some instances lower (e.g., for AUCt values) to those reported for the reference drug product.

In conclusion, the above information along with the lower degree of fluctuation in plasma NHP-554C SA concentrations at steady-state (Day 5) compared to the UPSA® Aspirin Hard Gelatin Capsules (325 mg) and the proposed once a day dosing regimen, support the controlled release designation claim for this product; provided that the ClinPharm and Clinical reviewing teams agree with the PD/efficacy/safety comparable performance of the drug product to the reference.

c) The in vitro Dose Dumping in the presence of Alcohol

The results of the in-vitro alcohol dose dumping studies showed that the integrity of the functional coating on the microparticles is compromised at high ethanol concentrations. This Reviewer presented the in vitro-alcohol dose-dumping results during the mid-cycle meeting that took place November 2014, and advised the reviewing team to evaluate the clinical relevance of the in-vitro alcohol dose-dumping results. The reviewing team revised the language in Section 17 Patient Counseling to inform patients of dose-dumping as follows:

"Alcohol Consumption: Inform patients they should not take DURLAZA 2 hours before or 1 hour after consuming alcohol. Counsel patients who drink three or more alcoholic drinks every day about the risk of bleeding involved in chronic, heavy alcohol use while taking DURLAZA."

d) Bridging Across Phases of Development

(b) (4)

[redacted]

(b) (4)

RECOMMENDATION:

The Division of Biopharmaceutics had reviewed the overall information submitted in the Original NDA 200671 and its amendments dated January 30, 2015, March 25, 2015 and April 28, 2015.

The following dissolution method and acceptance criteria for DURLAZA ER Capsules are deemed acceptable for batch release and stability testing:

Dissolution Method:

USP Apparatus II (Paddle) at 100 rpm,
900 ml of 0.05M Potassium Phosphate Buffer (pH 7.4) with trypsin and sodium azide at 37°C

Dissolution Acceptance Criteria:

1 hour: (b) (4)%
3 hour: %
9 hour: %
22 hour: %
30 hour: NLT (b) (4)%

From a Biopharmaceutics perspective NDA 200671 for DURLAZA, 162.5 mg is recommended for **APPROVAL**.

Kimberly Raines -S
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Date: 2015.05.04 17:14:02 -04'00'

Kimberly Raines, Ph. D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics, ONDP, OPQ

Sandra Suarez -A
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Date: 2015.05.04 21:13:34 -04'00'

Sandra Suarez Sharp, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics, ONDP, OPQ

Angelica Dorantes -S
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Angelica Dorantes, Ph.D.
Acting Branch Chief
Division of Biopharmaceutics, ONDP, OPQ

c.c.: PSeo, JDuan

BIOPHARMACEUTICS ASSESSMENT

INTRODUCTION

NHP-554C (DURLAZA), Extended Release Soft Gel Capsules is a controlled-release drug product composed of aspirin (acetylsalicylic acid, ASA) microparticles (particle size range [redacted]. The extended-release profile is achieved by using a [redacted] method to protect ASA in the gastrointestinal tract and sustain its release and activity for 24 hours. The [redacted] allows product release through diffusion, whereas the [redacted] that regulates product release. Formulation includes a 'loading dose' of approximately [redacted]% of the total dose to be delivered within the first three hours followed by sustained release for the remainder of the 24 hour period through diffusion.

[redacted] of ASA provides the following physiological advantages:

- Compatibility with the [redacted] process
- Time spent in the stomach is shorter and shows little sensitivity to gastric emptying, because even when closed, the pyloric sphincter will allow particles less than 1 mm in size to pass through.
- After disintegration, the microcapsules are more evenly distributed onto the surface of the intestine than when a tablet system is employed
- Dose dumping and local irritation are reduced

NHP-554C [redacted] is a controlled release product developed by [redacted] The initial formulation and manufacturing development work was conducted by [redacted] and is included in Module 3.2.P.2 Pharmaceutical Development of this submission. NHP-554C was acquired by New Haven Pharmaceuticals in 2009 and the manufacturing process was transferred to [redacted] facility in [redacted]

Drug Substance

Acetylsalicylic acid (ASA):

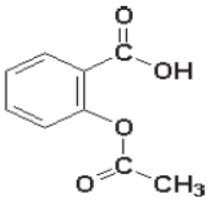

Figure 1. Chemical Structure of Acetylsalicylic acid

(b) (4)

ASA is slightly soluble in water, freely soluble in alcohol and soluble in chloroform and ether (Table 1).

ASA is considered a BCS Class 1/3 with poor solubility in acidic conditions of the stomach. Very little of ASA is ionized in the stomach after oral administration, which can delay absorption of high doses for eight to 24 hours. The increased pH and larger surface area of the small intestine causes ASA to be absorbed rapidly there, which in turn allows more of the salicylate to dissolve.

Table 1. Solubility of Acetylsalicylic acid

Water at	(b) (4)
Ethanol	(b) (4)
	(b) (4)

Drug Product

NHP-554C, Extended Release Capsules is a controlled-release drug product composed of aspirin (acetylsalicylic acid, ASA) microparticles, (b) (4)

(b) (4)

(b) (4) The composition of the extended release capsules are provided in Table 2 below.

Table 2: Composition of NHP-554C, Extended Release Capsules

Ingredient	Function	Unit Quantity (mg per unit)	Theoretical (%)	Theoretical quantity per batch (in kg)
Aspirin, USP	Active ingredient	162.5	(b) (4)	
Ethylcellulose, NF				
Povidone, USP				
Castor oil, NF				
Magnesium stearate, NF				
Tartaric acid, NF				
Colloidal anhydrous silica, NF				
Talc, USP				
Capsule 2 opaque white				
Theoretical capsule weight		(b) (4)		

Formulation Development

(b) (4)

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DISSOLUTION METHOD

The *in vitro* dissolution testing method that is being proposed as a quality control tool for DURLAZA, is summarized below:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)
ASA	ER Capsule	II (paddle)	100	0.05M Potassium Phosphate Buffer (pH 7.4) with trypsin and Sodium Azide with spiral sinker	900 mL, 37 °C

The dissolution method has remained the same through the phases of the product's development. The method as developed at (b) (4) was transferred to (b) (4).

DISSOLUTION METHOD DEVELOPMENT

(b) (4)

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data was *extrapolated* and the time was determined to be approximately 30 hours. The extrapolated 30 hrs was also confirmed in in vitro studies.

The following dissolution acceptance criteria were originally proposed by the Applicant as a QC for the release of DURLAZA:

Dissolution Acceptance Criteria
1 hour: NMT (b) (4) %
3 hour: (b) (4) %
(b) (4) hour: %
9 hour: %
(b) (4) hour: %
22 hour: NLT (b) (4) %

In response to Information Requests dated November 19, 2014 and April 24, 2015 the Applicant was asked to revise the acceptance criteria. The Applicant accepted the revised dissolution acceptance criteria proposed by the FDA as follows:

Dissolution Acceptance Criteria
1 hour: (b) (4) %
3 hour: %
9 hour: %
22 hour: %
30 hour: NLT (b) (4) %

EXTENDED RELEASE DESIGNATION CLAIM

According to the Applicant, the drug product was designed with an extended release profile capable of releasing the drug over a 24 hour period in order to inhibit thromboxane (detail for the selection of microcapsules is provided in Module 3, Section 3.2.P.2.1.2). The goal was to also suppress transfer of acetylsalicylic acid (ASA) into the systemic circulation. The formulation is designed to deliver diffusion-based drug delivery of acetylsalicylic acid which is characterized by the following factors:

(b) (4)

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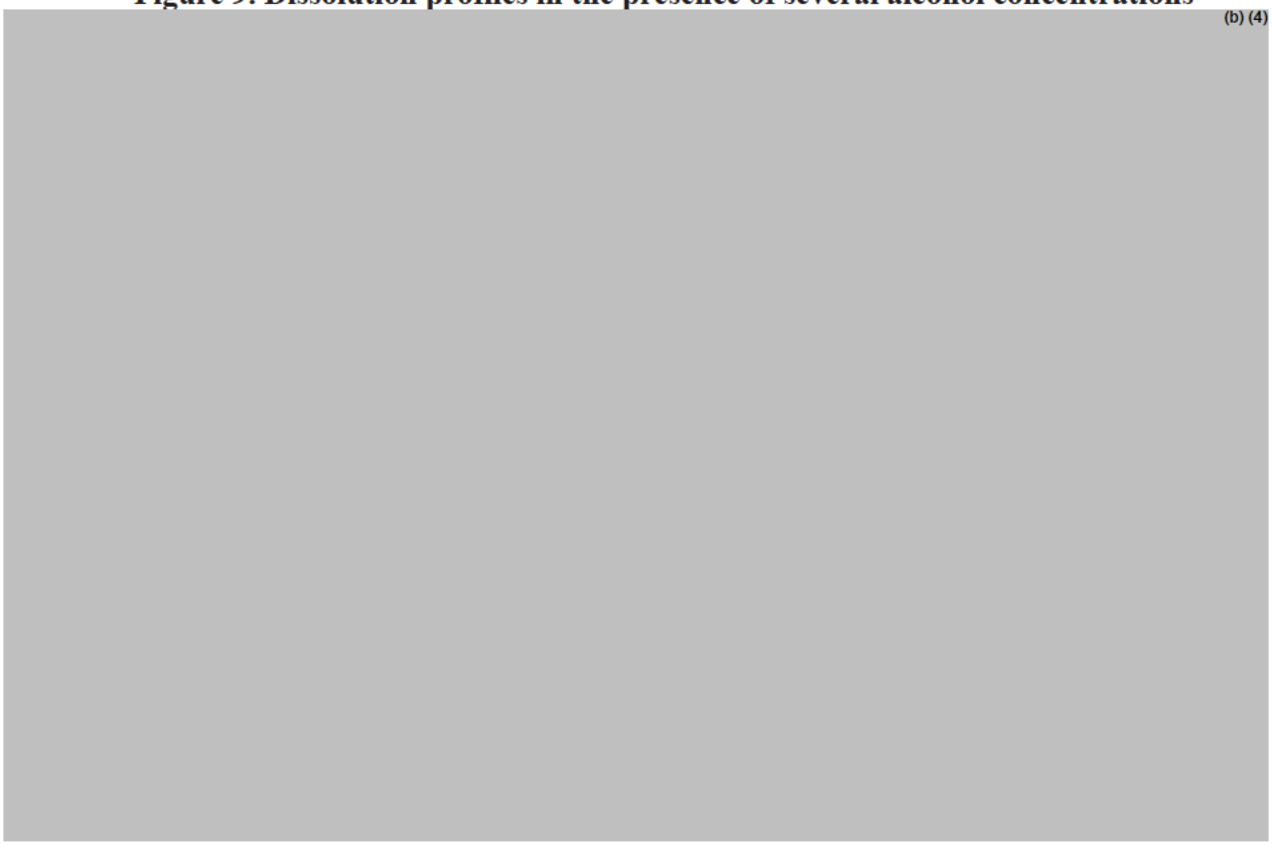
IN VITRO DOSE DUMPING IN THE PRESENCE OF ALCOHOL

The Applicant performed an Alcohol Dose-Dumping Study for 162.5 mg NHP-554C ASA ER Capsules. The study evaluated the potential for unintended rapid drug release in a short period of time in the presence of alcohol. The study was conducted with media 0.1N HCl and).1N HCl with 5%, 20%, and 40% ethanol with sampling times every 15 minutes for a 2 hour period (Figure 9).

Figure 9. Dissolution profiles in the presence of several alcohol concentrations

(b) (4)



Reviewer's Comments

This Reviewer presented the above in vitro-alcohol dose-dumping results during the NDA's mid-cycle meeting and conveyed the following comment to the review team during:

- *The clinical relevance of the in vitro alcohol dose-dumping results needs to be evaluated by the Office of Clinical Pharmacology and Office of New Drugs Clinical teams.*
- *New Haven Pharmaceuticals proposed to include the following language in its product labeling:*

(b) (4)

The review team revised the language in Section 17 Patient Counseling to remind prescribers to inform patients of dose-dumping as follows: "Alcohol Consumption: Inform patients they should not take DURLAZA 2 hours before or 1 hour after consuming alcohol. Counsel patients who drink three or more alcoholic drinks every day about the risk of bleeding involved in chronic, heavy alcohol use while taking DURLAZA [See Warnings and Precautions].

BRIDGING ACROSS PHASES OF DEVELOPMENT

(b) (4)

Figure 10. Summary of formulation development

Briefly, healthy Caucasian male subjects were enrolled in BE study PKFT 952 25 study. Twenty-four subjects completed the study, as one subject was excluded before dosing. The study products were well tolerated with no adverse effects reported. Bioequivalence was assessed for acetylsalicylic acid (ASA) and salicylic acid (SA), using three pharmacokinetic parameters: Cmax, Tmax, and AUC. The study was conducted according to Standard Operating Procedures. The study was conducted as an open-label, two-way crossover design with a washout period of two-weeks was respected between dosing. Subjects were dosed under fasting conditions. Blood samples were collected at pre-dose (0) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72 and 96 hours post-dose. Blood samples were analyzed for ASA and SA using a high performance liquid chromatography with UV detection assay. The bioanalytical standard operating procedure was provided within the submission.

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(b) (4)

[redacted]

CONCLUSIONS

The NDA is recommended for Approval from a Biopharmaceutics perspective.

The following dissolution method and acceptance criteria are deemed acceptable for release and on stability for DURLAZA ER Capsules.

Dissolution Method:

USP Apparatus II (Paddle), 100 rpm;
900 ml of 0.05M Potassium Phosphate Buffer (pH 7.4) with trypsin at 37°C

Dissolution Acceptance Criteria:

(b) (4)

1 hour: [redacted]%
3 hours: [redacted]%
9 hours: [redacted]%
22 hours [redacted]%
30 hour: NLT [redacted]%

It is noted that the above dissolution acceptance criteria were already agreed by the Applicant (refer to submission dated April 28, 2015).

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Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	200671	**NDA Submission Type**	505(b)(2)
OCP Division	I	**Brand Name**	DURLAZA
Medical Division	DCRP	**Generic Name**	Acetyl salicylic acid (ASA)
OCP Reviewer	Sudharshan Hariharan	**Drug Class**	Antiplatelet agent
OCP Team Leader	Rajanikanth Madabushi	**Indication(s)**	Secondary prevention of CV events
Pharmacometrics Reviewer	--	**Dosage Form/Strength**	Controlled release ASA microparticles in a capsule/162.5 mg
Date of Submission	09/05/2014	**Dosing Regimen**	Once daily
OCP Review Due	05/05/2015	**Route of Administration**	Oral
AC Meeting	--	**Sponsor**	New Haven Pharmaceuticals
PDUFA Due Date	07/05/2015	**Priority Classification**	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**	**1**	PK and PD [PKCR 0491]
multiple dose:	**X**	**4**	**4**	PK and PD [ASA-002, PKFT 97101, CLICR 30, CLICR 28]
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

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pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:	**X**	**2**	**2**	[U5A-96-02-001, U5A-96-02-002]
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	**1**	**1**	Dose-response study comparing controlled release vs IR aspirin in healthy volunteers [NHP-ASP-01]
Population Analyses -				
Pop PK				
Pop PK/PD				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**	**-**	ONDQA will review [PKFT 9542]
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**	**1**	PK and PD [ASA-001]
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	**X**	**1**	**-**	ONDQA will review
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**11**	**9**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	X			
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			Datasets are available in .xpt format for pivotal studies
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			
	Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)				
	Data				
11	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
12	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
13	Is the appropriate pharmacokinetic information submitted?	X			
14	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
15	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
16	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
17	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
18	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
19	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
20	Are the clinical pharmacology and biopharmaceutics studies of	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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	appropriate design and breadth of investigation to meet basic requirements for approvability of this product?				
21	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

Sudharshan Hariharan	10/27/2014
Reviewing Clinical Pharmacologist	Date
Rajanikanth Madabushi	10/27/2014
Team Leader/Supervisor	Date

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

/s/

SUDHARSHAN HARIHARAN
10/28/2014

RAJANIKANTH MADABUSHI
11/04/2014