

Entwicklung von Boswelan© als Phytopharmakon zur Remissionserhaltung beim M. Crohn

Tübingen, 5 April 2008

- Pharmazeutische Entwicklung (GMP)
- Präklinik (Toxikologie + Pharmakologie) (GLP)
- BfArM-Beratungsgespräch (Scientific Advice) (GLP+GMP+GCP)
- Klinische Entwicklung (GCP)

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Pharmazeutische Entwicklung (GMP)



Boswellia serrata Harz (Boswelliasäuren): aus indischem Anbau



Alkoholischer Extrakt (Ethanol 80 %): **FRUTAROM** Switzerland Ltd., Wädenswil (FRCH) (vormals Emil Flachsmann AG - EFLA) (Europäische Patentschrift Veröffentlichungsnummer 0 496 705 B1): „semifluid mass from its ethanol extract mixed with a polyethylene (Ph.Eur) as inert carrier”.



Boswelan Weichgelantinekapseln: **R.P. Scherer GmbH & Co. KG:**

Capsule shell: Ph. Eur.; Succinated Gelatine (capsule shell) in-house monograph; Red Iron Oxide (E 172), dye, NF; Titanium Dioxide (E 171), dye, Ph. Eu., USP; Riboflavin, dye, Ph. Eur.;

Active Ingredient per Kapsel: 400 mg native Boswellia serrata Resin Extract.

Packaging & GMP release certificate: **Catalent Germany Schorndorf GmbH** (vormals Cardinal Health Germany GmbH) (§ 6 and 7 PharmBetrV):

→ **Phytopharmakon (entwickelt wie NCE)**
(Prüfpräparat-spezifische Herstellungserlaubnis)



Prälinik: Toxikologie (GLP)

- **Boswellia serrata gum resin extract**
- **LPT Pharmacological/toxicological Expert Report (Directive 75/319/EEC as amended by Directives 83/570/EEC and 93/39/EEC) (November 23, 2000):**

The intended maximum dose in man at the start of the therapy is 3 x 3 - 4 tablets à 400 mg per day (3600 – 4800 mg/day). This corresponds to a maximum daily dose of 4800 mg corresponding to approximately 69 mg/kg b.w. for a 70 kg patient. The intended mean dose in man for a long-term treatment is 3 x 1 - 2 tablets à 400 mg per day (1200 to 2400 mg/day; corresponding to a maximum daily dose of approximately 34 mg/kg b.w..

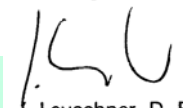
The acute toxicity was above 5000 mg/kg b.w. for the rat by oral administration.

Following repeated administration by gavage for 26 weeks (rat) and 9 months (dog), the no-effect level was 300 mg/kg b.w./day for the rat and 100 mg/kg b.w./day for the dog.

No mutagenic potential was observed

In conclusion, *Boswellia serrata* can be recommended for therapeutic use at the therapeutic dose levels given in this expert report. Though no teratogenic effects were observed in the reproduction studies, *Boswellia serrata* should only be used in pregnant and lactating women, in infants and small children when clearly needed.

Hamburg, November 23, 2000



J. Leuschner, D. Phil.
Expert Toxicologist DGPT

“

BfArM-Beratungsgespräch (24.6.2003) (GLP+GMP+GCP)

- **H15 (Gufic) Zulassungsantrag Fa. Ayurveda beim BGA (1992): Ablehnung wg. Schwermetall- und Cadmium-Verunreinigungen.**
- **Weihrauchextrakt = neuer Stoff, d.h. „volles Dossier“ nach NTA erforderlich.**
- **Drogenmonographie: Spezifikation als “Quantified Extract“ erwartet.**
- **Matrixspezifische Validierung der Bestimmung von Schwermetallen und Aflatoxinen.**
- **Vorschlag: Probandenstudie**



Frage:

- Ist davon auszugehen, dass - ein positives Ergebnis unterstellt - diese Studie ausreicht, um die geprüfte Indikation gewährt zu bekommen?



Antwort BfArM:

- Ein positives (also statistisch signifikantes) Ergebnis allein reicht nicht, sondern die Wirksamkeit muss überzeugend nachgewiesen werden. Siehe hierzu das CPMP Poits to Consider Dokument „PtC on application with 1. Meta-Analysis; 2. One Pivotal Trial (CPMP/EWP/2330/99) Ein Delta von 20 % (60 % Placebo Responder, 80 % Verum Responder) wäre ein sehr gutes Ergebnis. Wenn die Studie die Wirksamkeit überzeugend dokumentiert, reicht dies als Wirksamkeitsbeleg aus. Eine weitere Studie ist dann nicht erforderlich.



Klinische Entwicklung – Phase II-III

A multicenter, randomized, double-blind, placebo-controlled study of an orally administered „Boswellia serrata Extract PS0201Bo“ for maintaining remission of Crohn’s Disease.

- Principal Investigator:** PD Dr. med. Wolfgang Holtmeier, Chefarzt der Abteilung für Innere Medizin, Krankenhaus Porz am Rhein, Urbacher Weg 19, Köln (until 31.12.2007: QA am Zentrum der Inneren Medizin, Medizinische Klinik I, Klinikum der Johann Wolfgang Goethe-Universität)
- Sponsor:** Pharmasan GmbH Freiburg
- CRO:** CONVENTIS AG, Dr. med. Peter Klöpel, Am Campus 1-11, Rostock-Bentwisch, www.conventis.de

Klinische Entwicklung – Phase II-III

- **Investigator's Brochure:** 29.1. 2003 (*vorhandene Literatur + Boswelan-Herstellung*)

- **Dosisfindung via Literaturinformationen** (*top-down approach*)

- **Verträglichkeit von Weihrauchpräparaten:**

Basch et al, 2004:

*“most common complaints in trial - **nausea, acid reflux, mild gastrointestinal upset, diarrhea, skin irritations and dermatitis**”*

Arzneimittelkommission Oktober 2006 (gisela.schott@akdae.de):

*„Insgesamt haben wir in der Datenbank des deutschen Spontanmeldesystems (gemeinsame Datenbank von BfArM und AkdÄ, Stand 16.05.2006) **fünf Berichte** dazu identifizieren können. Davon betrifft je eine Meldung eine **Urtikaria**, eine **erhöhte gamma-GT**, **Fieber** und **Arthralgie** und zwei Berichte ein **Erythem**“*

- **BfArM-Vorlagebestätigung:** **Dezember 2003 (Vorlage-Nr.: 4021191; 10. AMG),
Fortführung der Studie: August 2006**

Klinische Entwicklung – Phase II-III

- **Design:** CPMP/EWP/2284/99: *Points to consider on clinical investigation of medicinal products for the management of Crohn's disease* & BfArM **Scientific Advice** & amended via **medical „State-of-Art“**
- **Patientenrekrutierung:**
 - Unterstützung durch DCCV (Studienaufruf) und Kompetenznetz-CED
 - öffentliche Werbung / Zeitungsanzeigen & CallCenter-Vorscreening (zentral)
- **Zustimmende Bewertung der Ethik-Kommission der Johann Wolfgang Goethe- Universität Frankfurt: (Geschäfts-Nr.: 26/03)**
 - Amendment 1: Juni 2006
 - Amendment 2: Oktober 2006
 - Amendment 3: Oktober 2007
- **BfArM-Vorlagebestätigung:** Dezember 2003 (Vorlage-Nr.: 4021191; 10. AMG)
Fortführung der Studie: August 2006 !

Klinische Entwicklung – Phase I

- **Investigator's Brochure:** 10.5.2006
- **Investigational Medicinal Product Dossier (IMPD):** PhytoLab GmbH & Co. KG, Vestenbergsgreuth
- **"Safety, tolerability and pharmacokinetics of a single dose application of two Boswellia serrata extract capsules in healthy male volunteers**
Open, randomized, cross-over pharmacokinetics (11-keto- β -boswellic acid – KBA - and acetyl-11-keto- β -boswellic acid - AKBA) after fasting or an standardized light breakfast.
- **Ethics Committee Johann Wolfgang Goethe-University Frankfurt favourable opinion, July 6, 2006 (Geschäfts-Nr.: 158/06)**
- **Higher Federal Authority, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM): Regulatory approval, EudraCT No: 2006-002939-24, Vorlage-Nr.: 4031905
Juli 18, 2006**

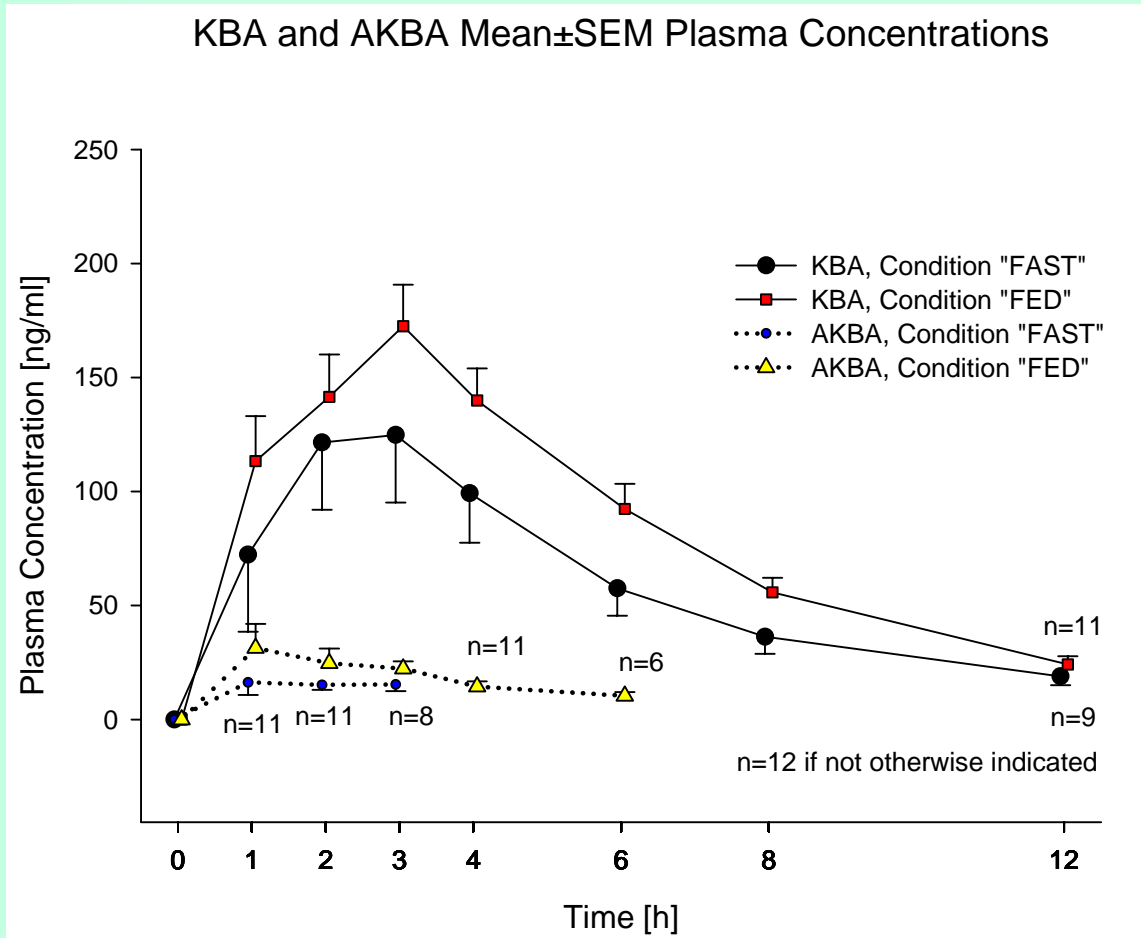


Klinische Entwicklung – Phase I

"Safety, tolerability and pharmacokinetics of a single dose application of two Boswellia serrata extract capsules in healthy male volunteers.

- Principal Investigator:** **Dr. med. Carsten Skarke**, Studienassistentz **Tina Homrighausen**
Studienzentrum Rhein-Main/ZAFES, Schleusenweg 22, Frankfurt / Main
- Investigators:** **Prof. Dr. med. Sebastian Harder**, **Dr. med. Karina Kuczka**, Institut für Klinische Pharmakologie, Klinikum der Johann Wolfgang Goethe Universität
- Analytics (KBA / AKBA):** **ACC GmbH Analytical Clinical Concepts**, **Dr. Bernhard Scheidel**
- Referenzsubstanzen:** **Prof. Dr. Johann Jauch**, Universität des Saarlandes, Organische Chemie II, Saarbrücken (*KBA / AKBA: analytical marker or active marker?*)
- LTB4 Immunoassay:** **IBL Gesellschaft für Immunchemie und Immunbiologie MBH**, Flughafenstrasse 52a, HAMBURG
- Cathepsin G:** **Prof. Dr. Oliver Werz**, Universität Tübingen, Pharmazeutisches Institut, Abteilung Pharmazeutische Analytik
- Sponsor:** **Claus Müller PhD**, **Pharmasan GmbH Freiburg**

Open, randomized, cross-over pharmacokinetics after fasting or breakfast



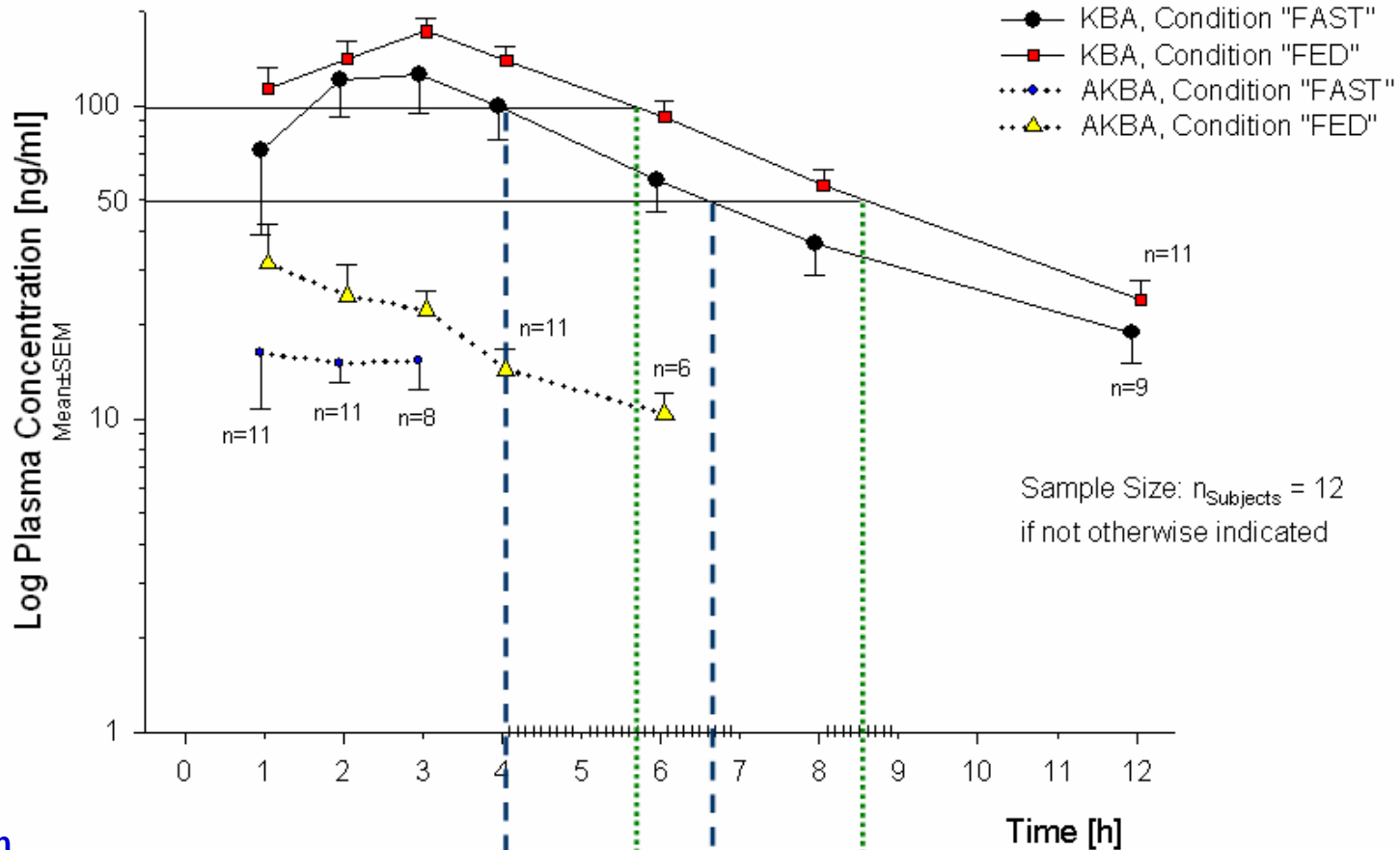
"Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products" (January 1, 2008)
<http://www.emea.europa.eu/pdfs/human/hmpc/25362907en.pdf>

C_{max} (AKBA, FAST): 0.029 μ M
 C_{max} (AKBA, FED): 0.058 μ M
(st.-st.: 3x2 caps/d 0.04 μ M)
 C_{max} (KBA, FAST): 0.260 μ M
 C_{max} (KBA, FED): 0.360 μ M
(st.-st.: 3x2 caps/d 0.3 μ M)

→ **Statistically significant food effect: increased oral KBA bioavailability by approx. 27%**

Mean±SEM KBA and AKBA log plasma concentration-versus-time curves after a single oral morning dose of 800 mg Boswelan after either a standardized breakfast (condition "fed") or after an overnight fasting period (condition "fast"); mean±SEM were constructed from n=12 healthy male volunteers if not otherwise indicated.

KBA and AKBA Mean±SEM Plasma Concentrations with Graphical Estimate on t_{1/2} of KBA



t_{1/2} AKBA „FED“ = 2.3 h

t_{1/2} AKBA „FAST“ = 1.3 h

KBA „FAST“
≈ 4.05 h

KBA „FAST“
≈ 6.65 h

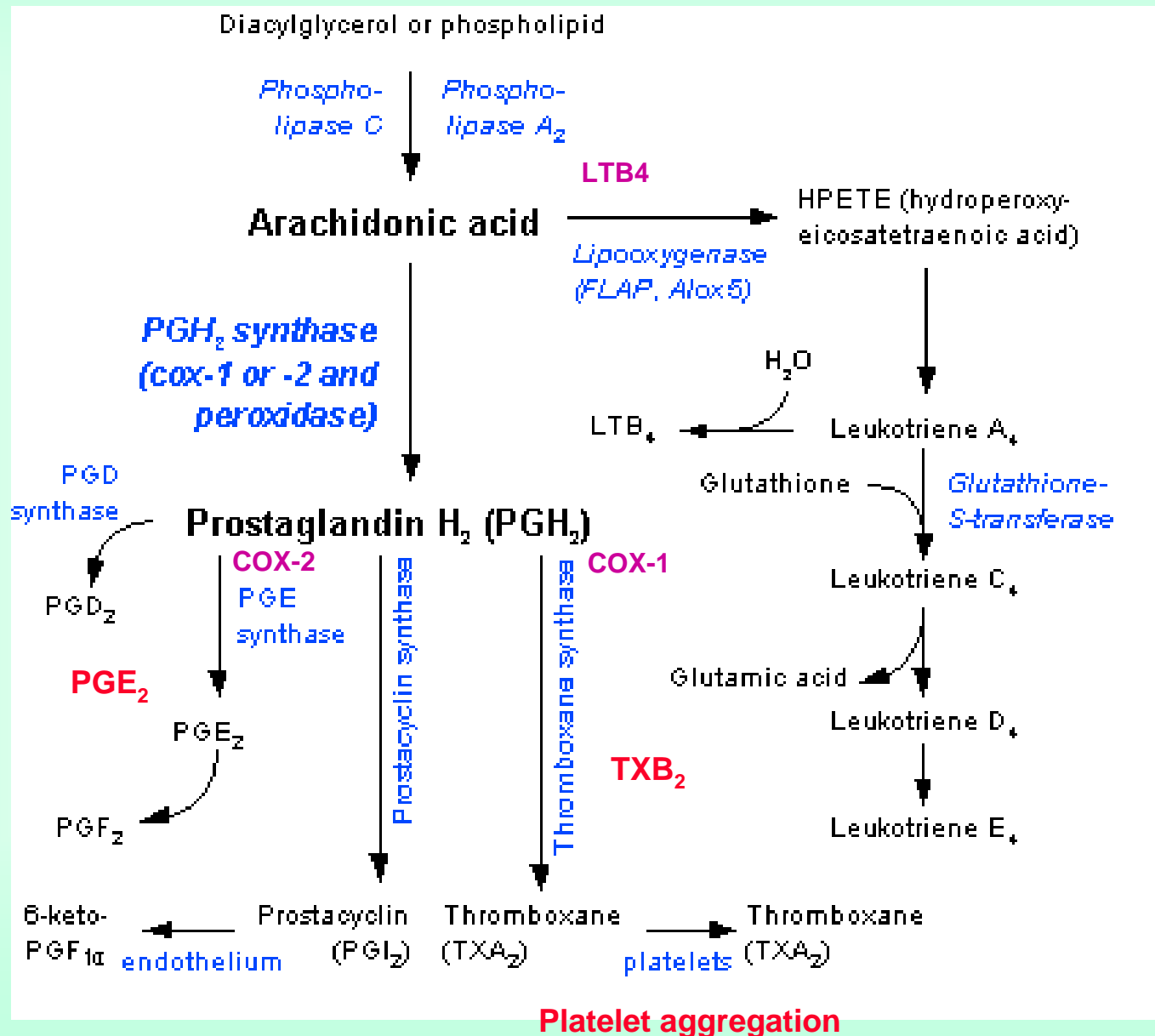
KBA „FED“
≈ 5.7 h

KBA „FED“
≈ 8.55 h

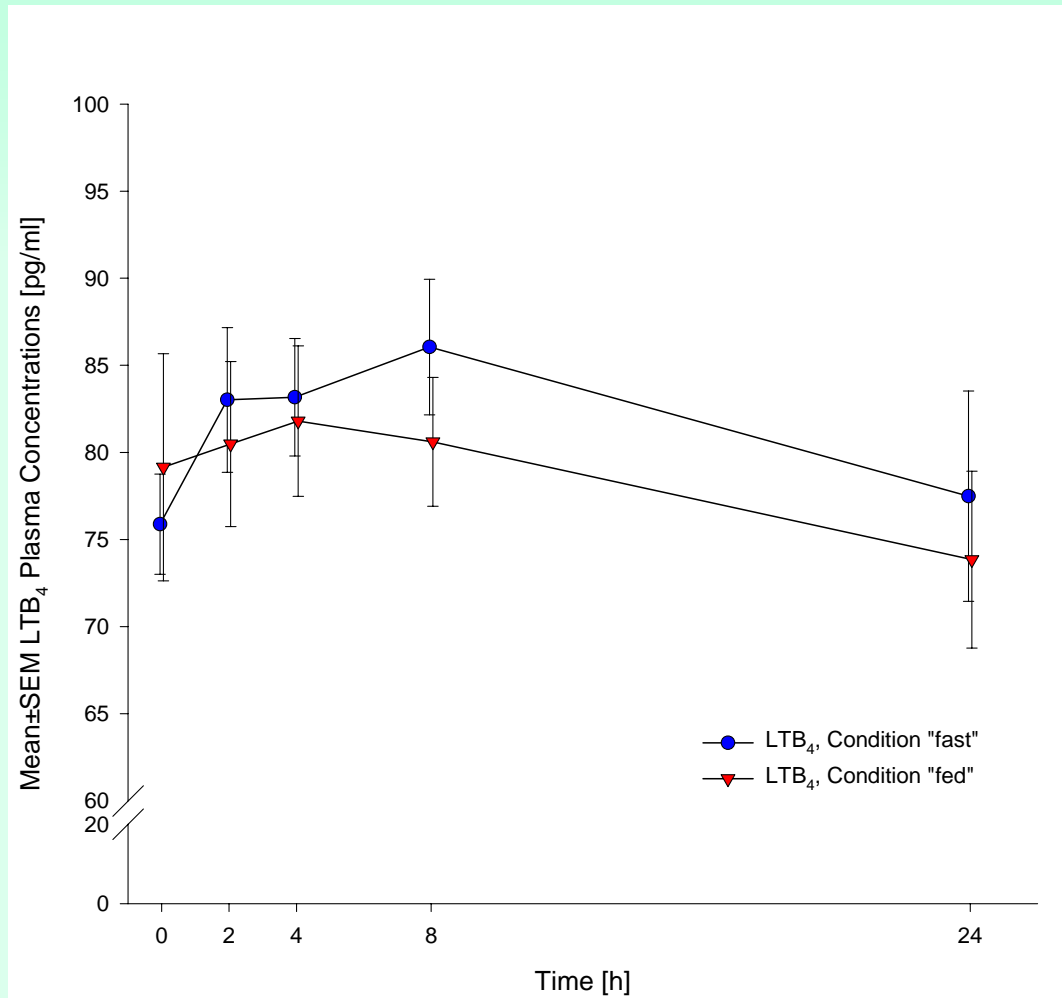
t_{1/2} KBA „FED“ ≈ 8.55 - 5.7 = 2.85 h

t_{1/2} KBA „FAST“ ≈ 6.65 - 4.05 = 2.6 h

Eicosanoid-Synthese und Boswelan©



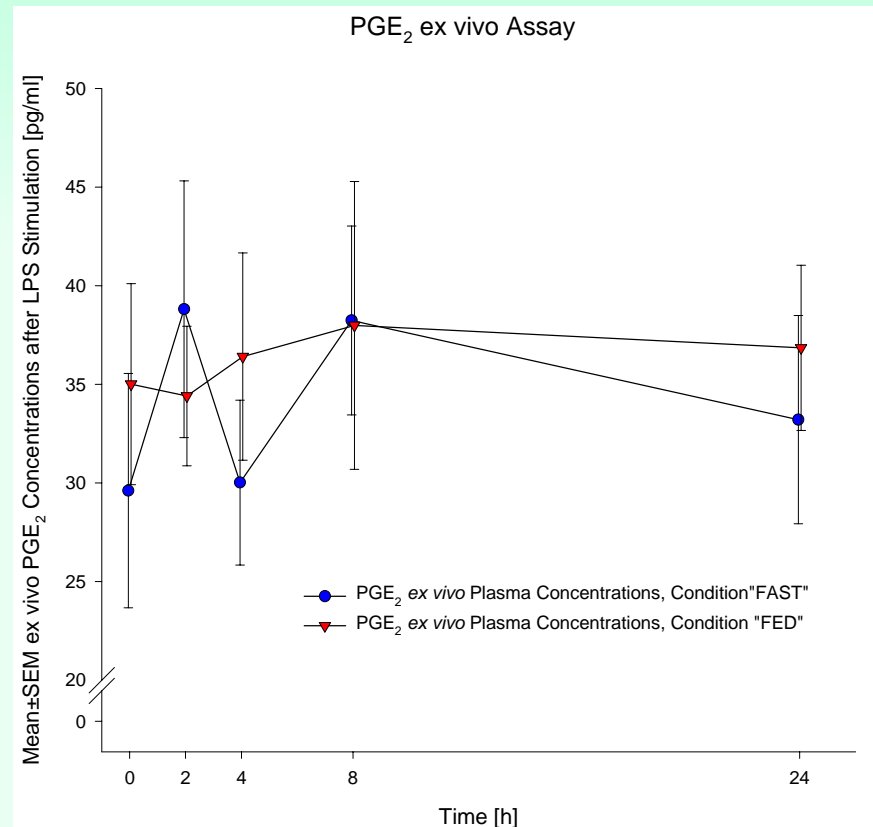
LTB₄



Mean ± SEM leucotrien B₂ (LTB₄) plasma concentration-versus-time curve after 800 mg native *Boswellia serrata* resin extract PS0201Bo either following a standardized breakfast (condition “fed”) or following an overnight fasting period (condition “fast”), n=12.

→ No clinically significant effects

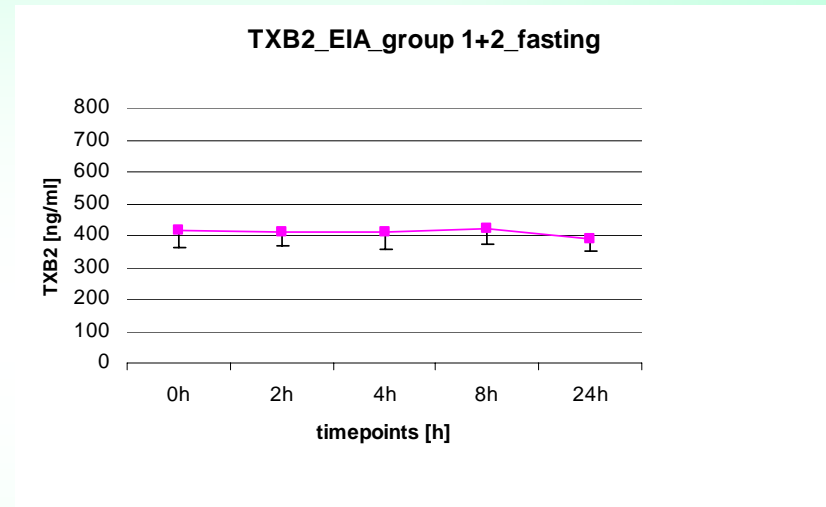
PGE₂ formation - surrogate for marker of the cyclooxygenase-2 (COX-2) activity



Mean±SEM prostaglandin E2 (PGE₂) concentration-versus-time curve after 800 mg native *Boswellia serrata* resin extract PS0201Bo either following a standardized breakfast (condition “fed”) or following an overnight fasting period (condition “fast”), n=12.

→ No significant or clinically relevant (anti-inflammatory) effects

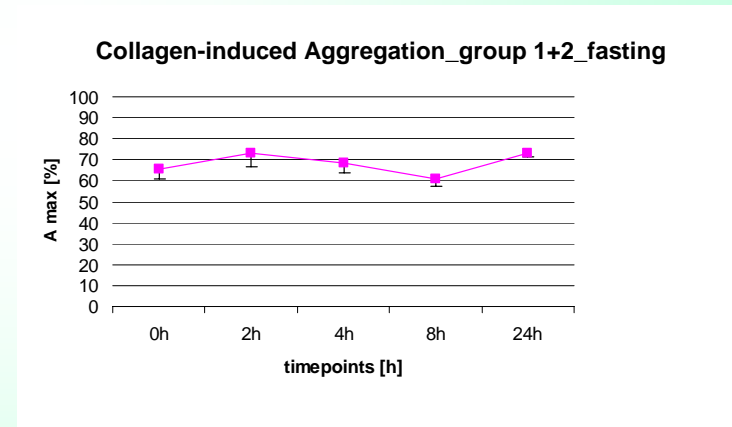
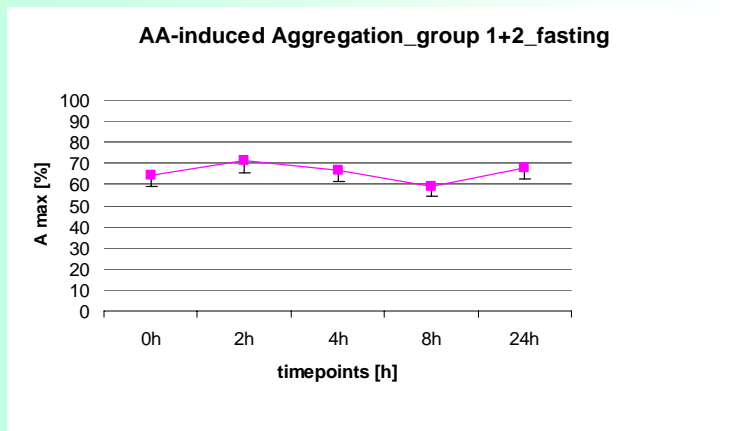
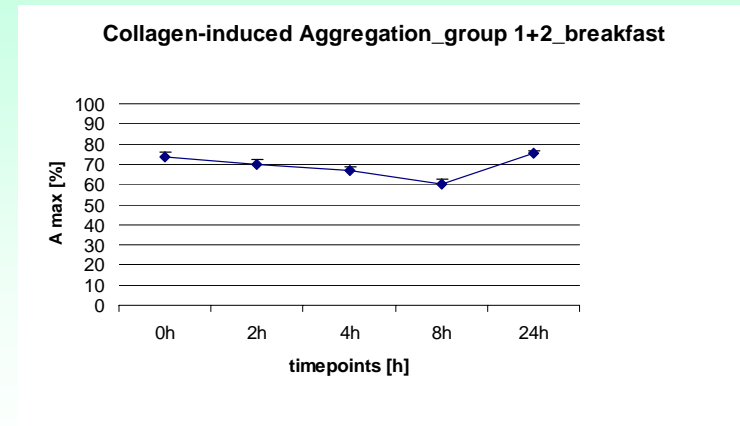
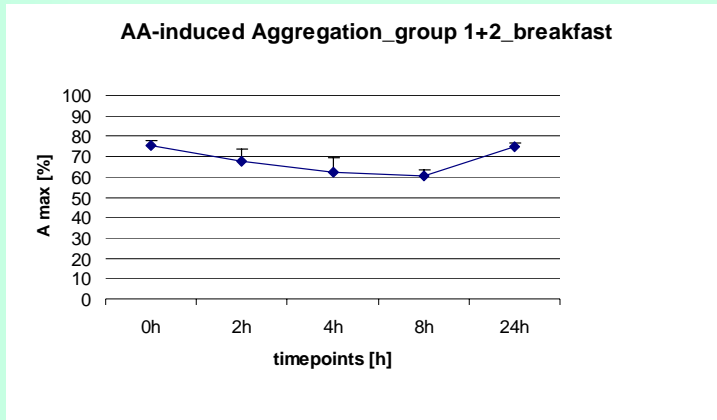
Tromboxan B₂ formation - surrogate marker for the cyclooxygenase-1 (COX-1) activity



Whole blood Thromboxane B₂ formation after application of 800mg boswellic acid after a standardized light breakfast or or following an overnight fasting period n=12.

→ No significant or clinically relevant (anti-inflammatory) effects

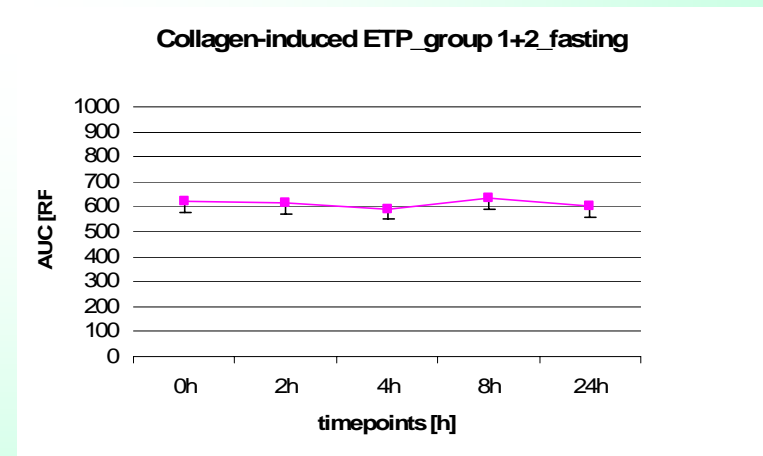
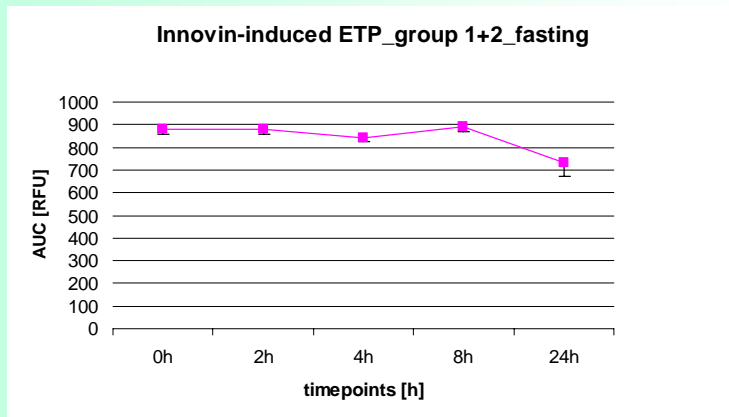
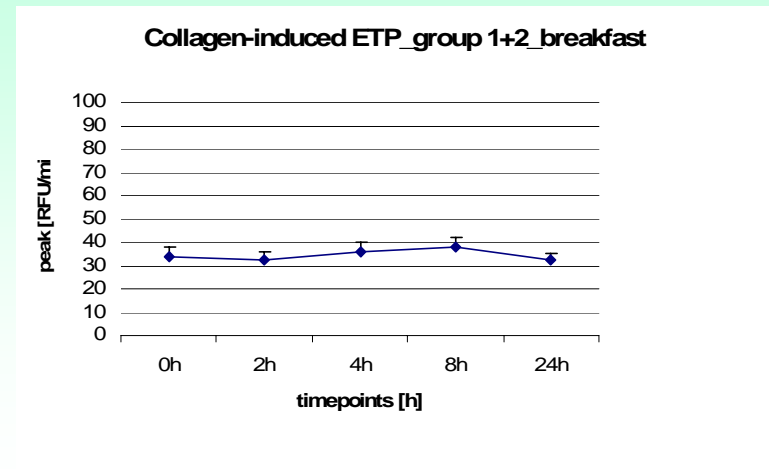
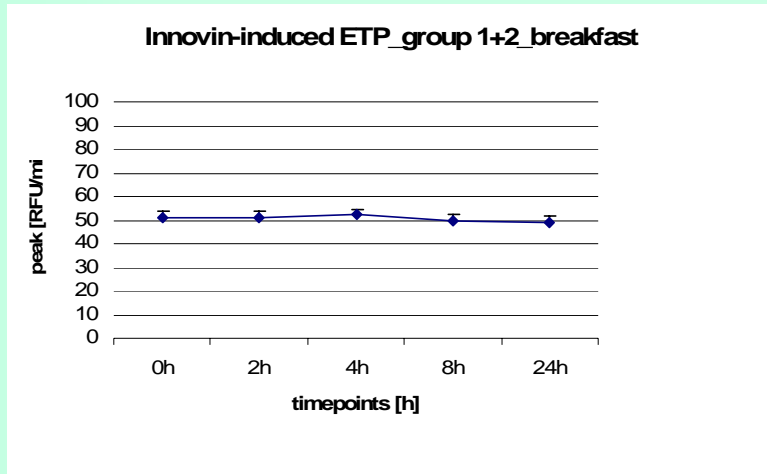
Platelet aggregation



Arachidonic acid- and collagen-stimulated platelet aggregation after application of 800mg boswellic acid after standardized light breakfast and in fasting state and (mean values and SEM for both groups summarized)

➔ No significant or clinically relevant effects

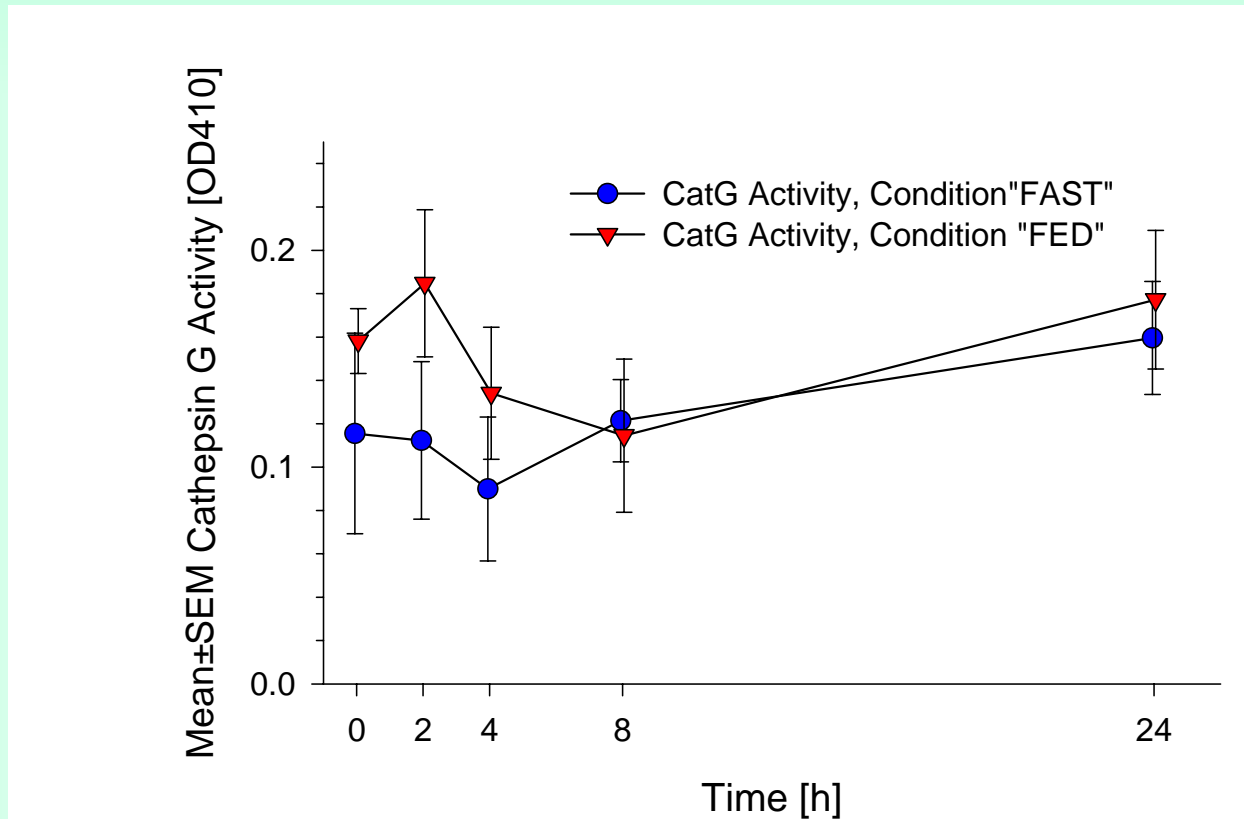
Innovin- and collagen-induced thrombin generation



Innovin- and collagen-induced thrombin generation (peak) after application of 800mg boswellic acid after a standardized light breakfast or following an overnight fasting period (condition “fast”) (mean values and SEM for both groups summarized).

➔ No significant or clinically relevant effects

Cathepsin G activity



Cathepsin G activity in plasma expressed as increase of absorption at 410 nm caused by substrate conversion. Subjects received 800 mg native *Boswellia serrata* resin extract PS0201Bo either following a standardized breakfast (condition “fed”) or following an overnight fasting period (condition “fast”) and venous blood was taken and analyzed for cathepsin G activity after indicated times, n=12.

→ Statistically significant effects