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)

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Präklinik: 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.

BfArM

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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)

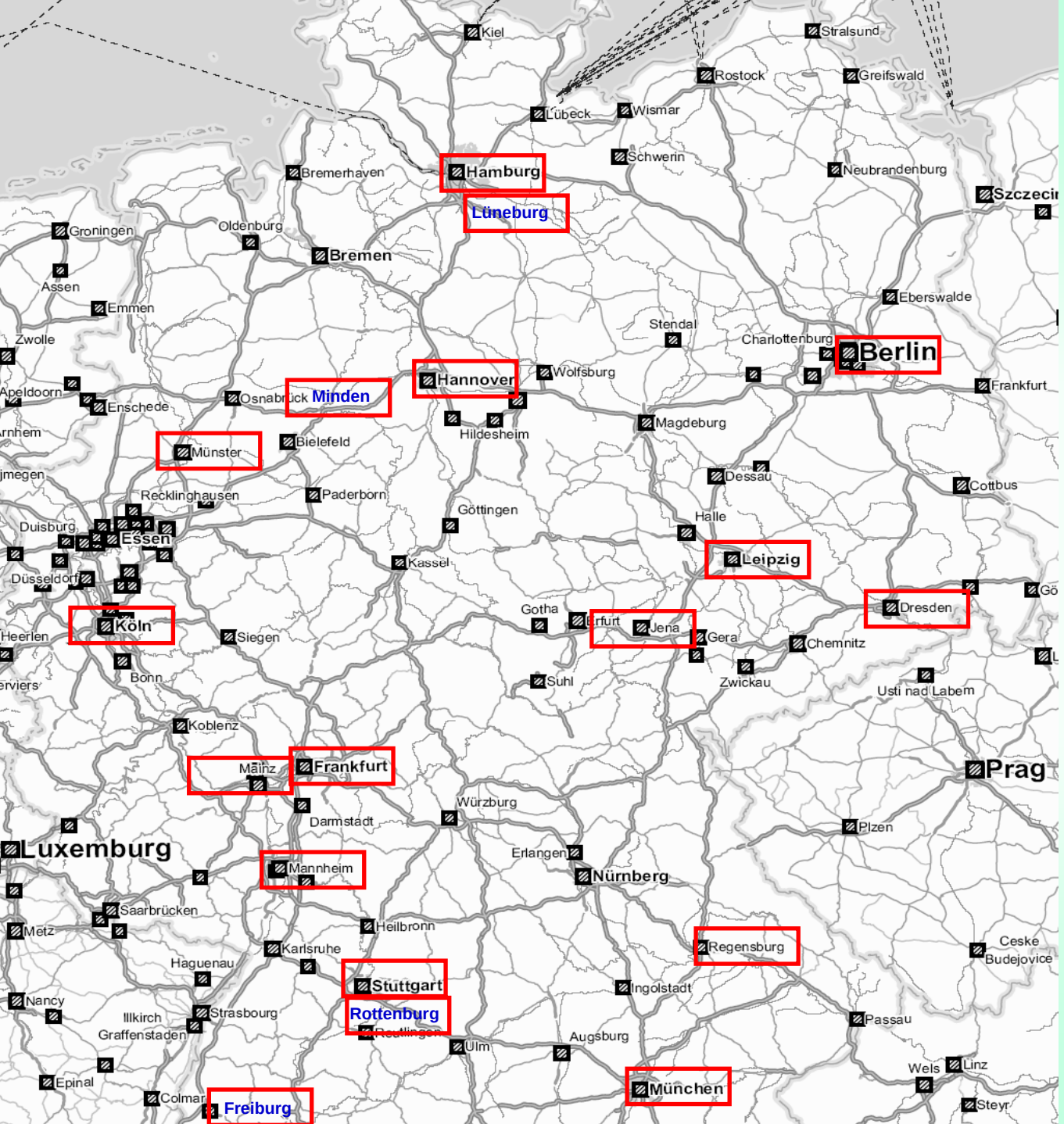
- **Zustimmende Bewertung der Ethik-Kommission der Johann Wolfgang Goethe- Universität Frankfurt: (Geschäfts-Nr.: 26/03)**

  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 !



Advisory Board:
Prof. Caspary, Frankfurt
Prof. Zeitz, Berlin
LKP: PD Dr. Holtmeier

25 Zentren	**# Patienten**
Berlin 1, Prof.	**(7)**
Berlin 2, PD Dr.	
Berlin 3, Prof.	**(2)**
Dresden, Prof.	
Frankfurt 1, PD Dr.	(**15**)
Frankfurt 2, Prof.	
Freiburg, Prof.	
Hamburg 1, Prof.	**(3)**
Hamburg 2, Dr.	**(1)**
Hamburg 3, Prof.	
Hannover, Prof.	
Jena, Prof.	**(2)**
Köln, Prof.	**(8)**
Leipzig, PD Dr.	**(1)**
Lüneburg, Dr.	
Mannheim, Dr.	
Mainz, Dr.	**(5)**
Minden, Dr.	**(1)**
München 1, PD Dr.	
München 2, Prof.	**(2)**
Münster 1, Dr.	**(10)**
Münster 2, Dr.	**(4)**
Regensburg, Dr.	**(1)**
Stuttgart, Prof.	
Rottenburg, Dr. F.	**(3)**

Screened: 106; randomisiert: **# 65**

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-ß-boswellic acid – KBA - and acetyl-11-keto-ß-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**

KLINISCHES STUDIENZENTRUM RHEIN-MAIN ZAFES

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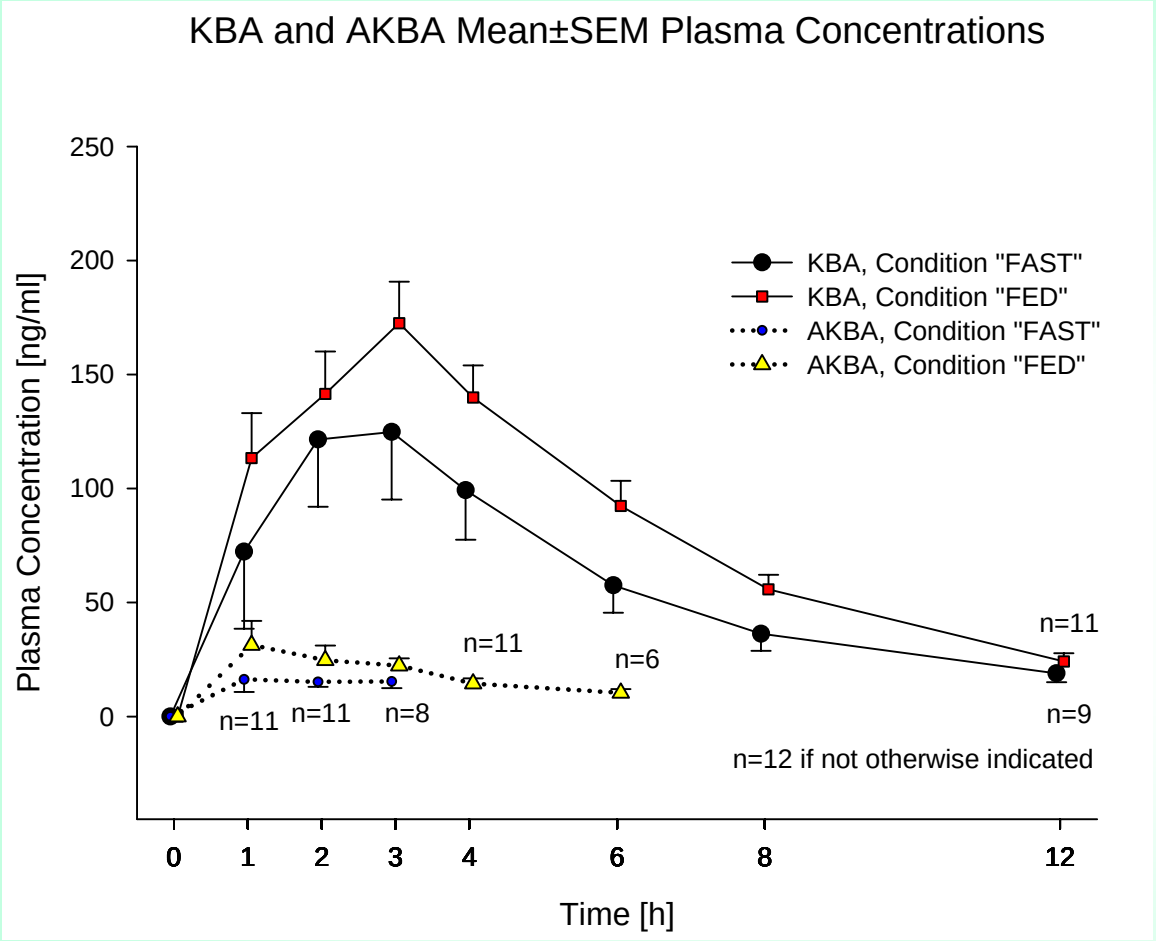
Klinische Entwicklung – Phase I

"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,** Studienassistenz **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 µM
C_{max} (AKBA, FED): 0.058 µM
(st.-st.: 3x2 caps/d 0.04 µM)
C_{max} (KBA, FAST): 0.260 µM
C_{max} (KBA, FED): 0.360 µM
(st.-st.: 3x2 caps/d 0.3 µM)

➔ 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.

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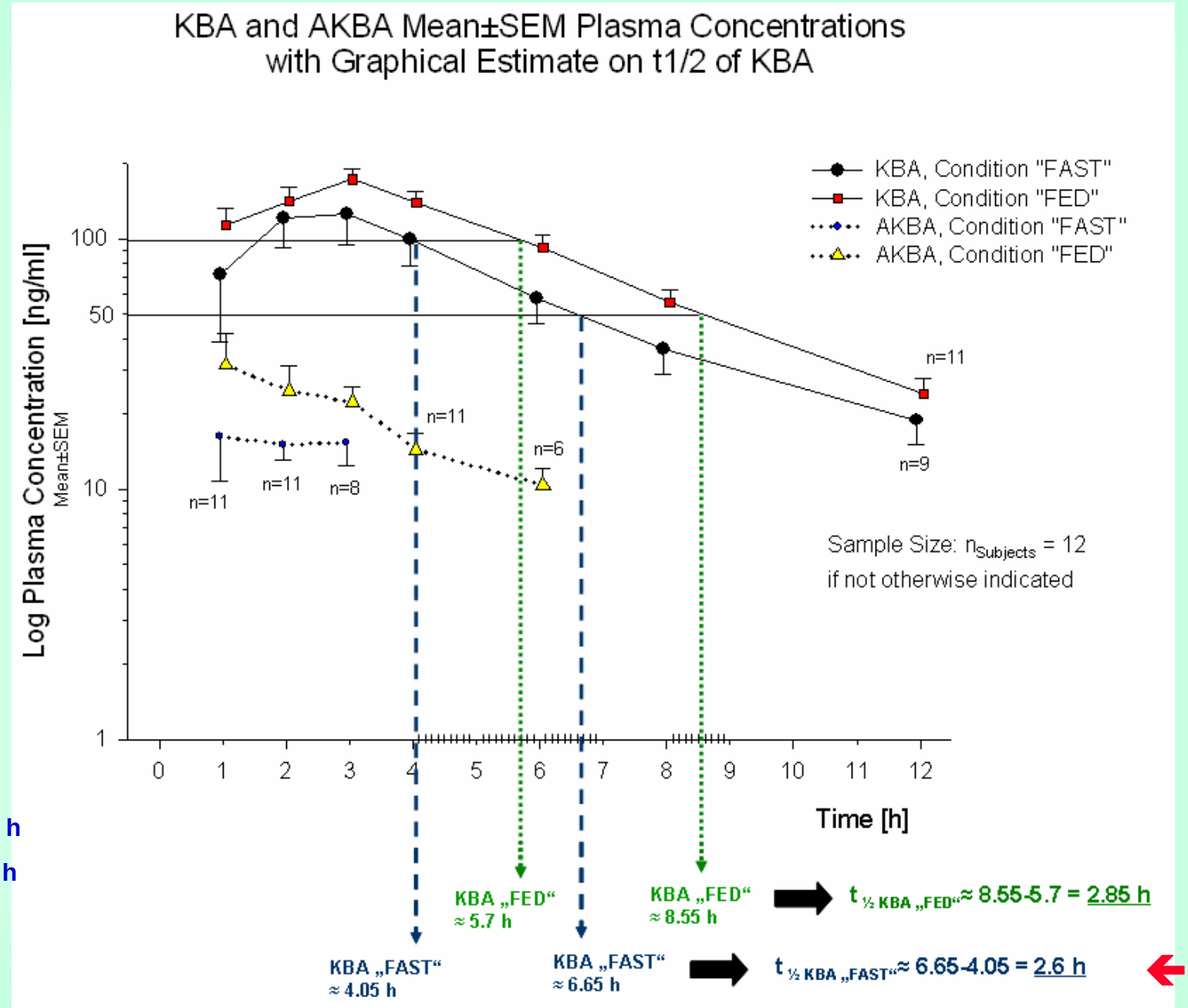

$t_{1/2\ AKBA\ „FED“}$ = 2.3 h

$t_{1/2\ AKBA\ „FAST“}$ = 1.3 h

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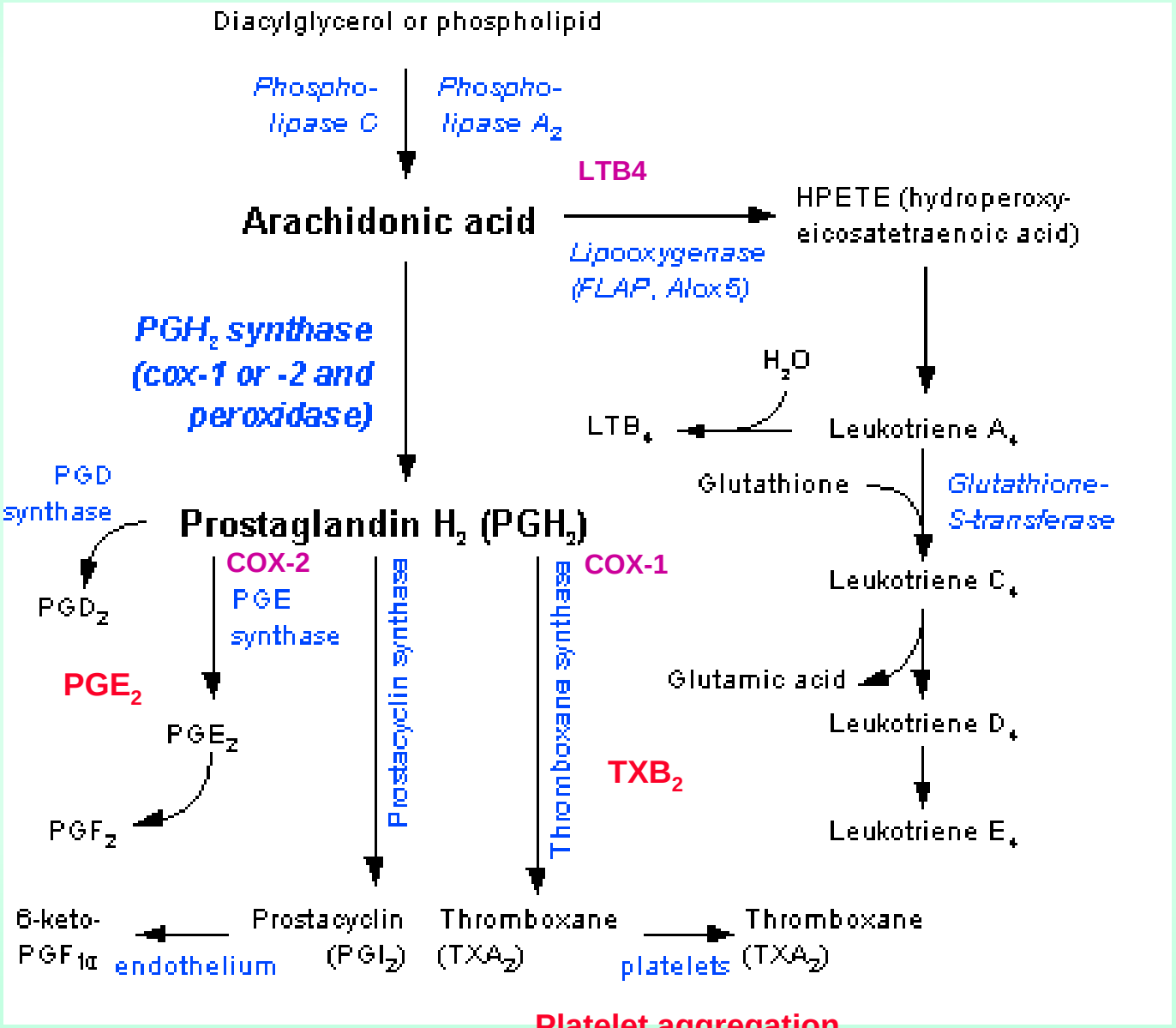
Eicosanoid-Synthese und Boswelan©



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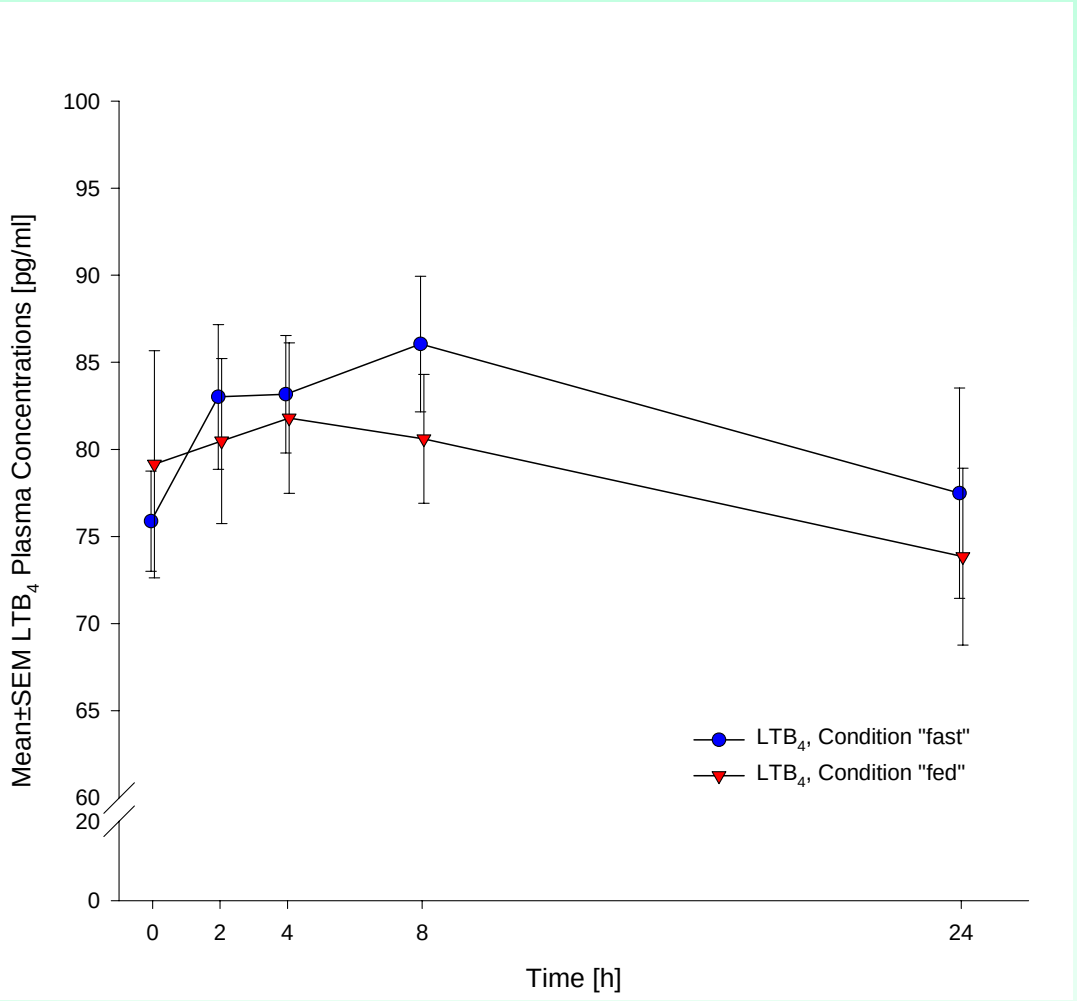
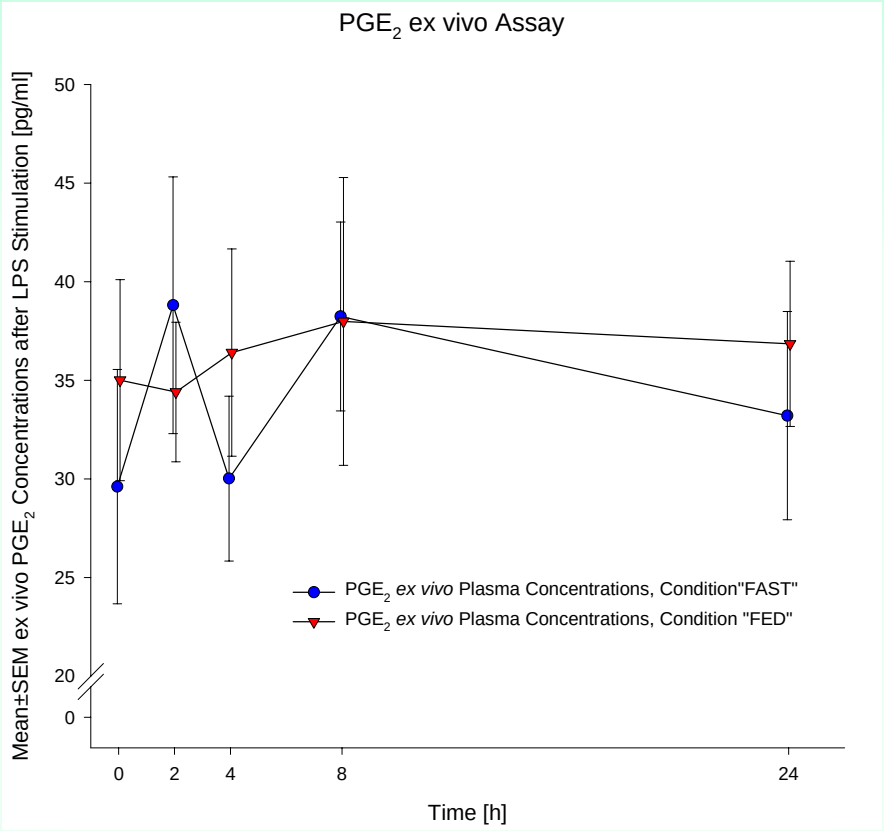
LTB4



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**

PGE_2 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

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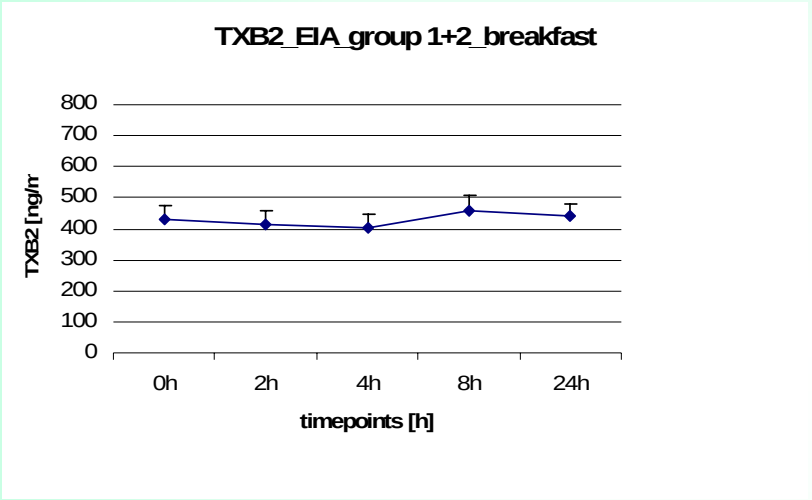
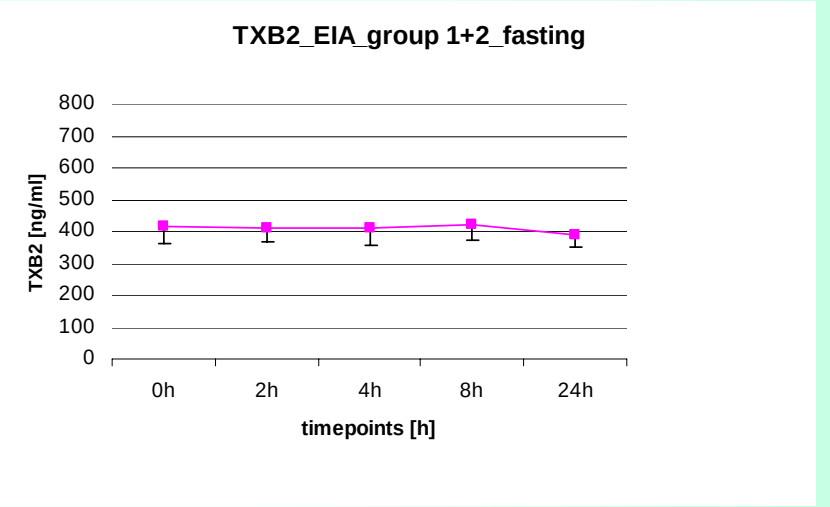
Tromboxan B_2 formation - surrogate marker for the cyclooxygenase-1 (COX-1) activity





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**

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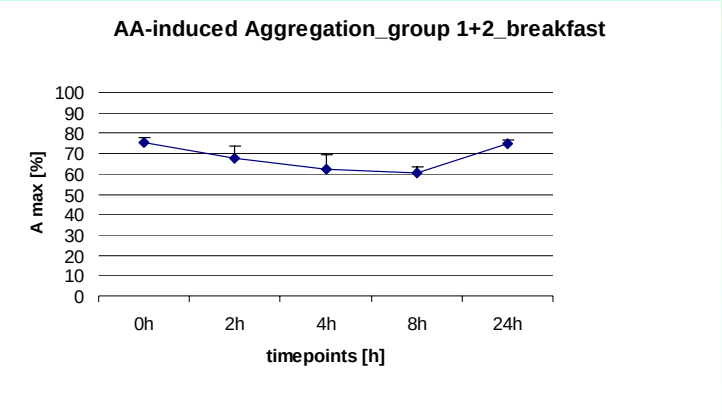
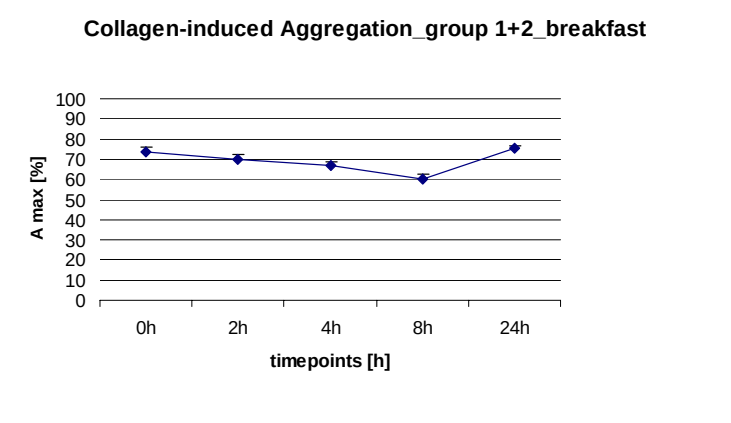
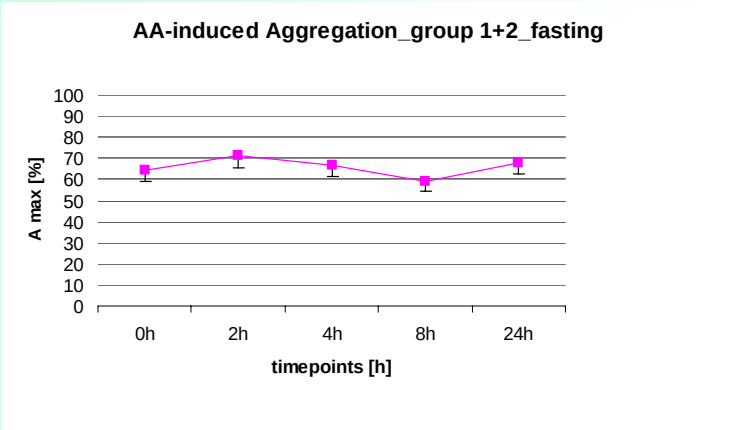
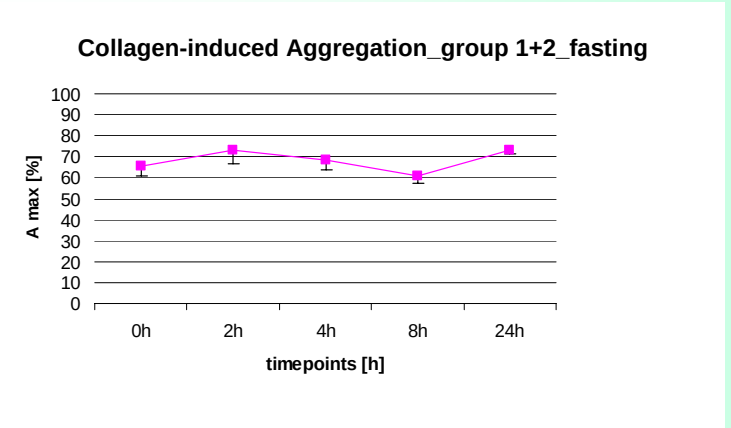
Platelet aggregation









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

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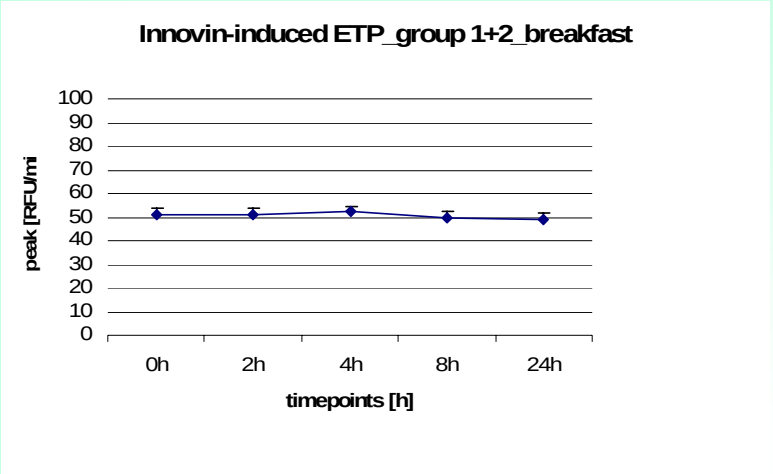
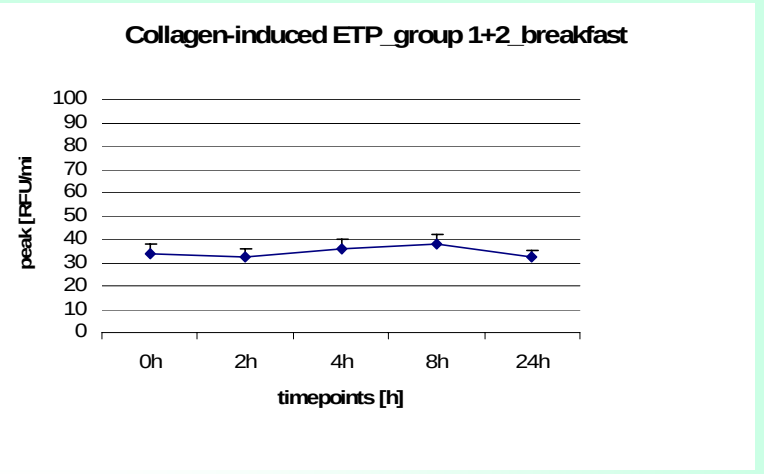
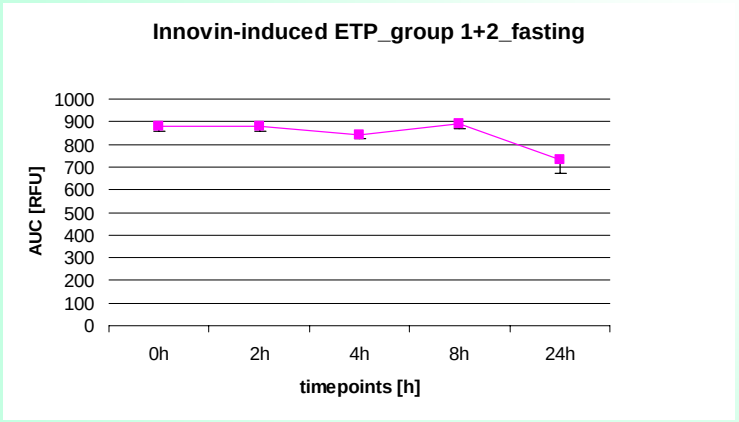
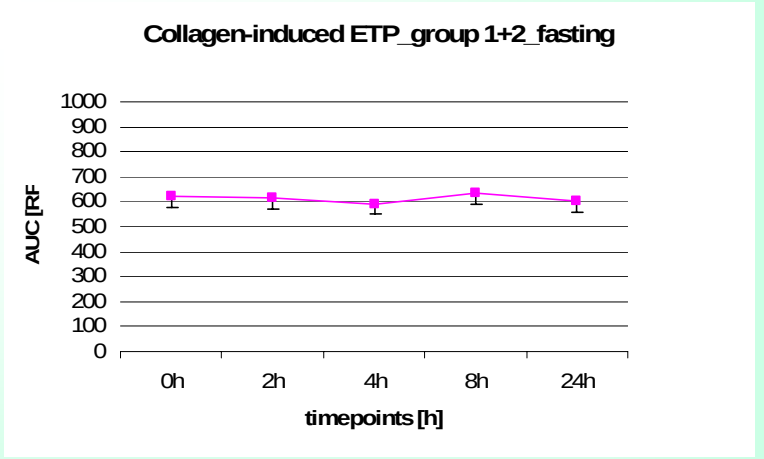
Innovin- and collagen-induced thrombin generation









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

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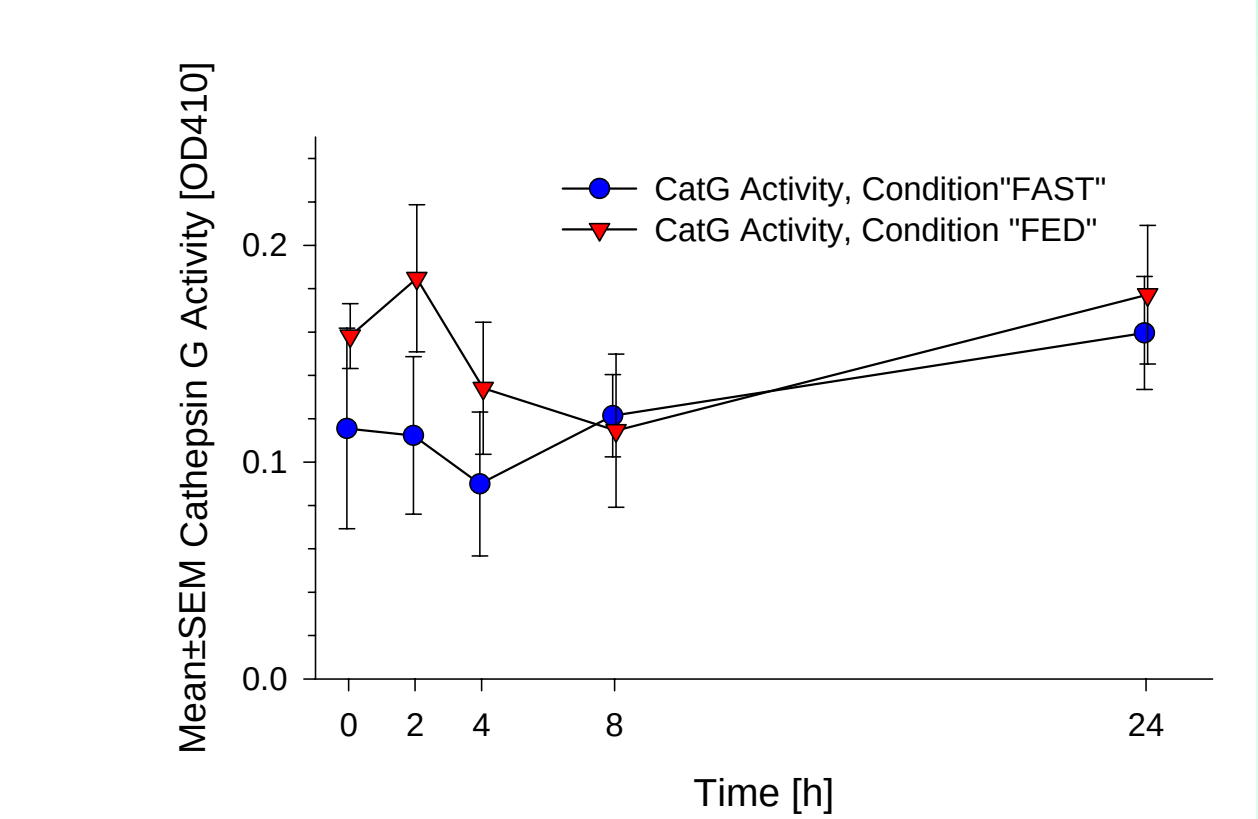
Cathepsin G activity



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