**Supplemental table files**

**Supplemental table 1:** Histological characteristics of the donors.

**Supplemental table II:** PCR primers used in the study.

**Supplemental table III:** Effect of gender on CYP3A4 activity, protein and mRNA expression.

**Supplemental table IV:** Predicted pharmacokinetic parameters (Geometric mean, 95% CI) after 5 mg intravenous dose in populations accounting for fatty liver.

**Supplemental table V:** Predicted pharmacokinetic parameters (Geometric mean, 95% CI) after 5 mg intravenous dose in populations accounting for fatty liver and insulin resistance.

**Supplemental figure files**

**Supplemental figure I.** Scheme of the histological scoring system used for group formation in the study.

**Supplemental figure II.** Correlation of CYP3A4 activity with (A) CYP3A4 mRNA and (B) CYP3A4 protein. (C) Correlation between CYP3A4 mRNA and protein expression. *P<0.05* were considered significant. Correlation coefficient represents Spearman r. Messenger RNA data expressed relative to 18S rRNA. Some parameters were $\log_{10}$ transformed for graphical representation.

**Supplemental figure III.** Effect of different grades of steatosis (A) NADPH cytochrome P450 reductase protein, and (B) Cytochrome b5 protein. Column and error bars represent mean ± SE. *$P$<0.05 as compared to <5% liver fat. *$P$-values reported from nonparametric Kruskal-Wallis test (2-sided) without adjustment for multiple comparisons.

**Supplemental figure IV:** Spearman correlation analysis of age with (A) CYP3A4 activity (pmol/min/mg protein), (B) CLint (L/min), (C) CYP3A4 protein (pmol/mg protein) and (D) CYP3A4 mRNA. *P<0.05* was considered significant. Correlation coefficient represents Spearman r. Messenger RNA data expressed relative to 18S rRNA. Closed circles represent normal, open circles represent NAFL and triangles represent NASH samples.

**Supplemental figure V.** Association of NADPH-cytochrome P450 reductase with (A) CYP3A4 activity (pmol/min/mg protein) and (B) CYP3A4 protein (pmol/mg protein). Correlation of cytochrome b5 with (C) CYP3A4 activity (pmol/min/mg protein) and (D) CYP3A4 protein (pmol/mg protein). (E) Correlation between NADPH-cytochrome P450 reductase and cytochrome b5 proteins. *P<0.05* was considered significant. Correlation coefficient represents Spearman r. Messenger RNA data expressed relative to 18S rRNA. Some parameters were $\log_{10}$ transformed for graphical representation.

**Supplemental tables**

| Supplemental table 1: Histological characteristics of donors | | | |
|---|---|---|---|
| **Histological score** | **Normal** | **NAFL** | **NASH** |
| | **n=24** | **n=26** | **n=24** |
| **Steatosis** | | | |
| 0 | 24 | 0 | 0 |
| 1 | 0 | 12 | 7 |
| 2 | 0 | 7 | 7 |
| 3 | 0 | 7 | 10 |
| **Hepatocyte ballooning** | | | |
| 0 | 23 | 19 | 0 |
| 1 | 1 | 6 | 18 |
| 2 | 0 | 1 | 6 |
| **Lobular inflammation** | | | |
| 0 | 9 | 9 | 0 |
| 1 | 12 | 13 | 18 |
| 2 | 3 | 4 | 6 |
| **Fibrosis** | | | |
| 0 | 12 | 10 | 8 |
| 1 | 9 | 11 | 12 |
| 2 | 2 | 4 | 3 |
| 3 | 1 | 1 | 1 |
| **Diabetic** | 11 | 14 | 11 |
| **Non-diabetic** | 13 | 12 | 13 |

**Supplemental table II: PCR primers used in the study**

| Gene | Primer type | Primer Sequence | Length | GC number | GC % | Tm |
|---|---|---|---|---|---|---|
| **CYP3A4** | Forward | CTTTTATGATGGTCAACAGCCTGTG | 25 | 11 | 44 | 58.8 |
| | Reverse | CTTTTCATAAATCCCACTGGACCA | 24 | 10 | 42 | 57.1 |
| **CYP3A5** | Forward | CCCACACCTCTGCCTTTG | 18 | 11 | 61 | 58.1 |
| | Reverse | CAGGGAGTTGACCTTCATACG | 21 | 11 | 52 | 58.5 |
| **PXR** | Forward | GCTGACAGAGGAGCAGCGGATGA | 23 | 14 | 61 | 64.0 |
| | Reverse | CCCTGGCAGCCGGAAATTCTT | 21 | 12 | 57 | 60.4 |
| **CAR** | Reverse | AGATGGAGCCCGTGTGGG | 18 | 12 | 67 | 60.4 |
| | Forward | GGTAACTCCAGGTCGGTCAGG | 21 | 13 | 62 | 62.4 |
| **HNF4α** | Reverse | CTGCTCGGAGCCACCAAGAGATCCATG | 27 | 16 | 59 | 66.6 |
| | Forward | ATCATCTGCCAGGTGATGCTCTGCA | 25 | 13 | 52 | 62.1 |
| **PPARα** | Reverse | CCAGTATTTAGGAAGCTGTCCTG | 23 | 11 | 48 | 58.7 |
| | Forward | CGTTGTGTGACATCCCGACAG | 21 | 12 | 57 | 60.4 |
| **18S rRNA** | Reverse | CGCCGCTAGAGGTGAAATTC | 20 | 11 | 55 | 58.4 |
| | Forward | TTGGCAAATGCTTTCGCTC | 19 | 9 | 47 | 53.9 |

**Supplemental table III: Effect of gender on activity, protein and mRNA expression**

| **Gender** | Female | Male |
|---|---|---|
| **Sample size (n)** | 38 | 36 |
| **Vmax (pmol/min/mg protein)** | 303.95±84.21 | 368.95±74.42 |
| **Km (μM)** | 1.96±0.18 | 1.96±0.25 |
| **Clint, whole liver (L/min)** | 3.03±0.96 | 4.79±1.17 |
| **CYP3A4 (pmol/mg protein)** | 73.71±13.54 | 100.66±14.71 |
| **CPR (pmol/mg protein)** | 40.60±2.01 | 44.15±2.12 |
| **Cyb5 (pmol/mg protein)** | 505.66±19.32 | 618.40±33.41 |
| **CYP3A4 mRNA[1]** | 5.41±1.88 | 6.03±1.62 |
| **CAR mRNA[1]** | 1.94±0.24 | 2.76±0.73 |
| **PXR mRNA[1]** | 1.98±0.25 | 1.87±0.24 |
| **HNF4α mRNA[1]** | 1.81±0.31 | 1.56±0.24 |
| **PPARα mRNA[1]** | 1.33±0.20 | 1.21±0.24 |

All descriptive statistics value represent mean±SE. *$P$<0.05 as compared to normal liver. P-values reported from non-parametric Mann-Whitney U test (2-sided). [1]Messenger RNA data expressed relative to 18S rRNA

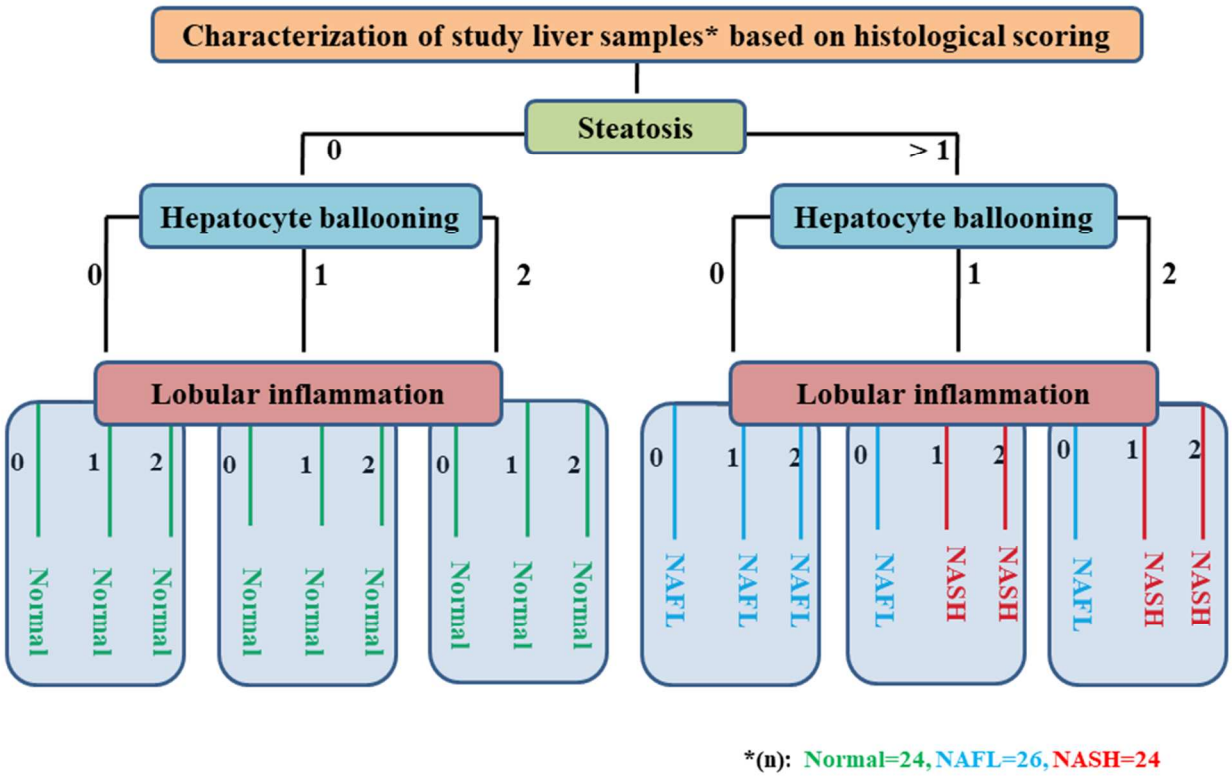
**Supplemental table IV: Predicted pharmacokinetic parameters (Geometric mean, 95% CI) after 5 mg intravenous dose in virtual populations (n=250 in each group) accounting for fatty liver.**

| | Normal | NAFL | NASH |
|---|---|---|---|
| **$C_{max}$ (ng/mL)** | 114.8 (107.7-122.4) | 114.8 (107.7-122.4) | 114.8 (107.7-122.4) |
| **$AUC_{0-24}$ (ng/mL.h)** | 301.3 (280.3-323.9) | 533.5 (492.2-578.3) | 680.7 (634.9-729.7) |
| **CL (L/h)** | 16.6 (15.4-17.8) | 9.4 (8.6-10.2) | 8.6 (6.8-7.9) |

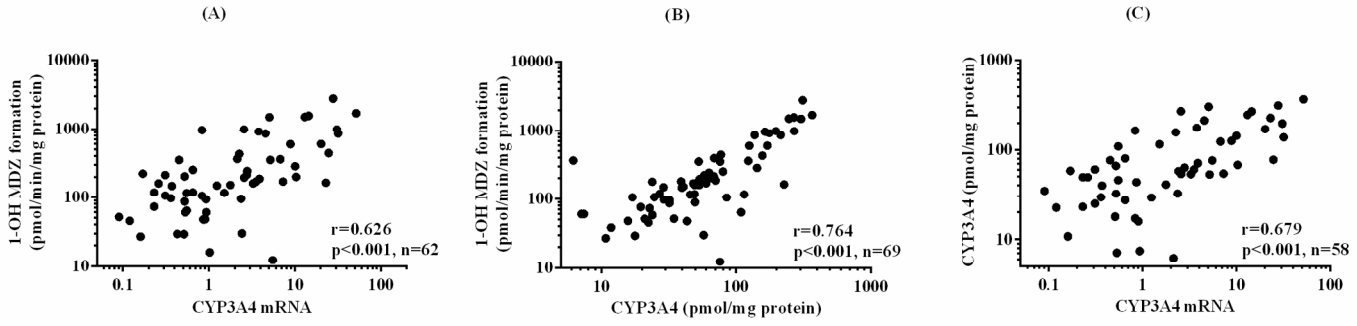
**Supplemental table V: Predicted pharmacokinetic parameters (Geometric mean, 95% CI) after 5 mg intravenous dose in virtual populations (n=250 in each group) accounting for fatty liver and diabetes.**

| | Non-diabetic | | | Diabetic | | |
|---|---|---|---|---|---|---|
| | **Normal** | **NAFL** | **NASH** | **Normal** | **NAFL** | **NASH** |
| **$C_{max}$ (ng/mL)** | 114.8 (107.7-122.4) | 114.8 (107.7-122.4) | 114.8 (107.7-122.4) | 114.8 (107.7-122.4) | 114.8 (107.7-122.4) | 114.8 (107.7-122.4) |
| **$AUC_{0-24}$ (ng/mL.h)** | 363.1 (334.5-394.2) | 436.4 (404.0-471.5) | 584.8 (546.3-626.0) | 252.7 (237.6-268.7) | 660.1 (618.8-704.3) | 769.0 (729.3-810.9) |
| **CL (L/h)** | 13.8 (12.7-14.9) | 11.5 (10.6-12.4) | 8.6 (8.0-9.2) | 19.8 (18.6-21.0) | 7.6 (7.1-8.1) | 6.5 (6.2-6.9) |

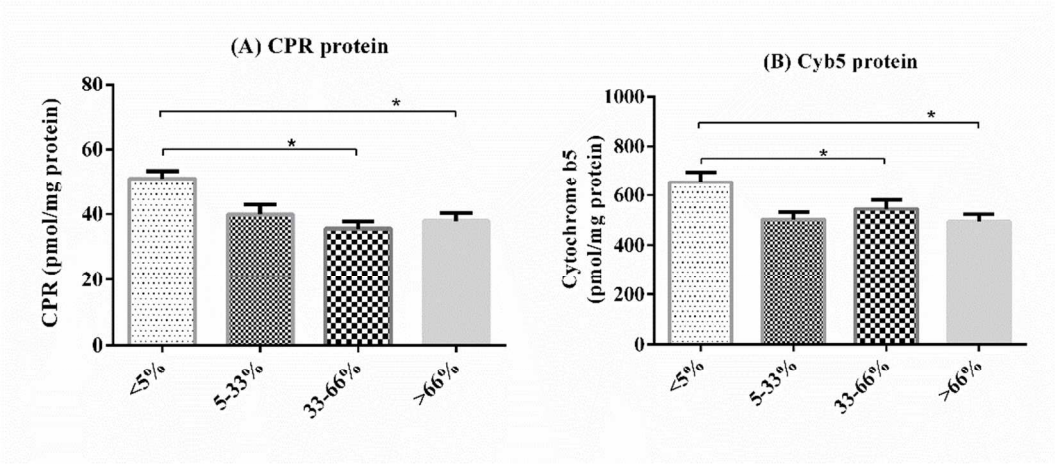
**Supplemental figures**



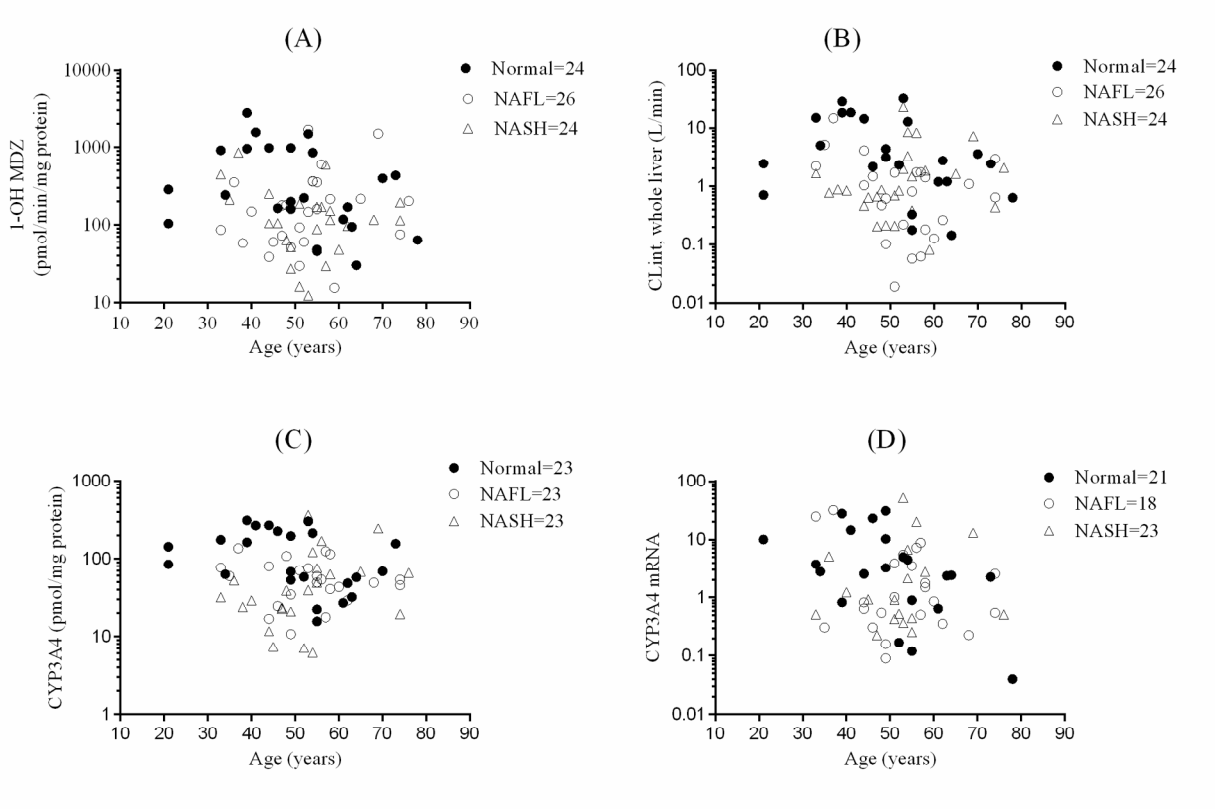

**Supplemental figure I**



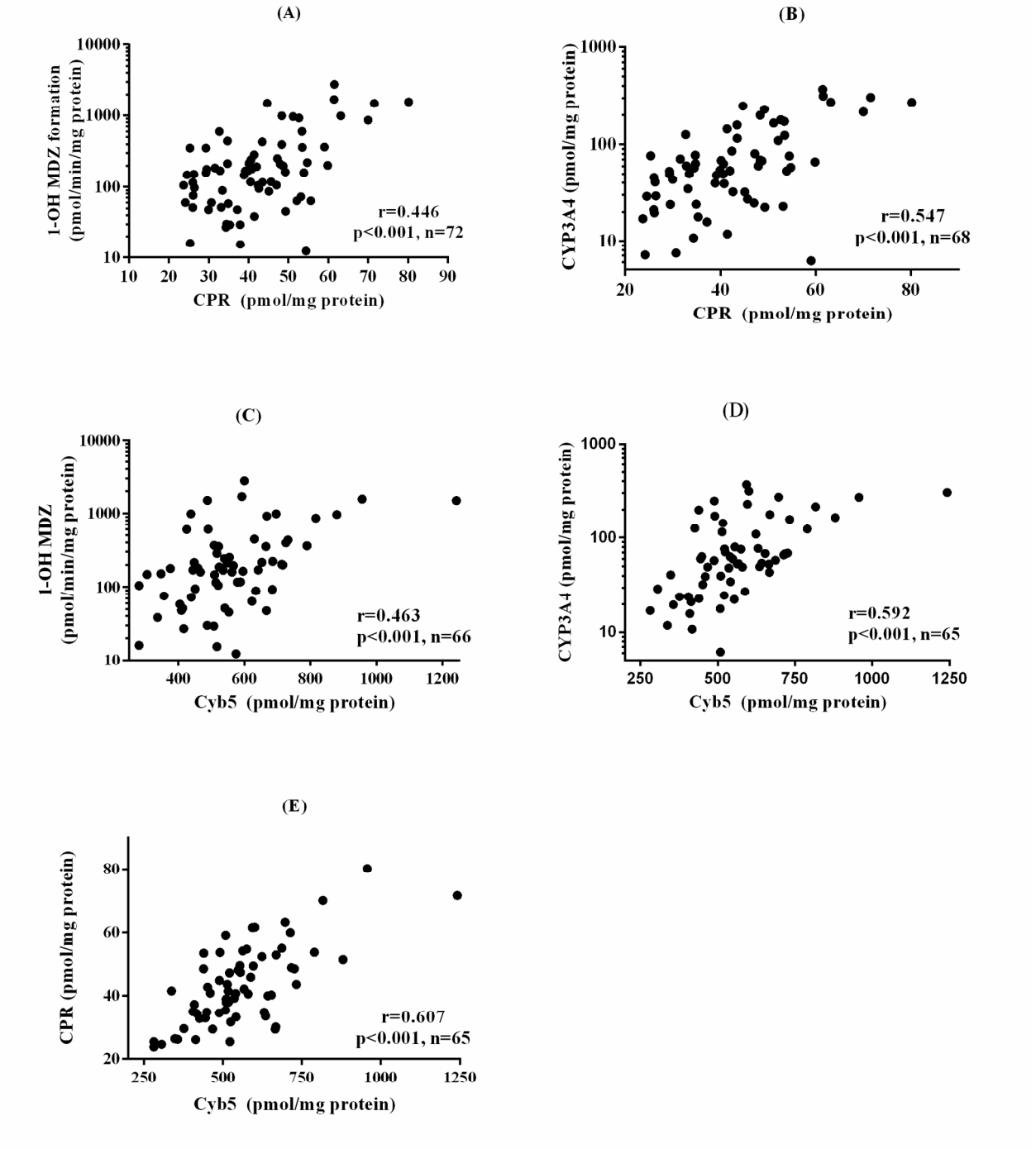
**Supplemental figure II.**




**Supplemental figure III.**




**Supplemental figure IV.**




**Supplemental figure V.**